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Open for innovation

Sophie Roberts explores more creative R&D approaches to plugging the holes in big pharma's product pipelines

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In recent years, there has been a substantial shift in direction in the R&D sector of the pharmaceutical industry. Dwindling pipelines alongside the threat of generic drug companies rising through the slats has put big pharma into overdrive as they turn to externalisation more than ever before. In this article, the term externalisation, will umbrella both in and out-licensing, collaborations, and mergers and acquisitions.

Externalisation is not foreign ground for big pharma. Since the boom of drug discovery and development, big pharmaceuticals have always, in one or way another, undertaken externalisation. Before the demise of the blockbuster model, they worked behind an archetype of closed innovation to retain the upmost control over their IP. But, the pharmaceutical landscape has shifted, and gone are the thriving blockbuster days of the late 1980s and early 1990s when a radical new drug would be discovered internally and developed internally to generate billions in sales. The time to look elsewhere has never been more urgent and although externalisation between pharmaceuticals, biotechs and areas of academia has always occurred, in the last five years, choice has turned into necessity.

Out of the myriad elements that are involved in bringing a drug to market from early in-house R&D, there are two reasons in particular that are key drivers: cost and deteriorating pipelines. The enormous financial pressure of internally seeing a drug right through from its early stages to market is a major driving force behind looking elsewhere to lower that cost and advance scientifically more quickly. Making a drug that would stand out amongst the rest during a time of advancing technology and when knowledge in specialist areas was rapidly growing, was also a distinct challenge. Channelling the right ideas, with the right funds, technology and resources to come up with replacement, next generation drugs is imperative for big pharma to survive.

A shift in direction

What we are now witnessing is a large scale back of early R&D in big pharmaceutical companies, and growth in external, collaborative and licensed R&D in all stages of drug development. As Dr Richard Baker, director general of The Association of the British Pharmaceutical Institute (ABPI), puts it in a blog, "Life sciences in Britain is an ecosystem, involving academic research, SMEs and larger companies, working ever more closely together. But all of them are under pressure and in the process of change."

Nothing quite demonstrated this shift in direction the way Pfizer did when it announced that it was planning to close down its R&D facility in Sandwich, UK earlier this year. However, by no means is Pfizer the only pharmaceutical company to act in this way. Many of the leading pharmaceutical companies have closed down internal R&D facilities to pursue early R&D using collaborations or further down the line in-licensing deals. Mergers and acquisitions have also become a popular route as big pharma looks to dynamically fill their product portfolios and harness unused IP.

Big pharmaceuticals such as GlaxoSmithKline (GSK), Pfizer, AstraZeneca and Sanofi-Aventis have all been pioneers in the changing pharmaceutical landscape, and it's not just in UK where change is happening. There has been a global shift in pharmaceutical priorities to cope with erosion of market sales.

With help from external resources, holes in product pipelines can be filled with next generation IP which will lead to next generation scientific opportunities. "At the end of the day, we want to gain access to the science that will help in driving our business forward," said Dr Malcolm Skingle, academic liaison for GlaxoSmithKline. "We are trying to get more shots on goal by accessing a broader range of scientific approaches." It is essential for big pharma's survival to keep up the flow of proprietory drugs. Two of the more frequently used methods of doing this are through in-licensing and collaborations.

In-licensing opportunities

In-licensing is a partnership that develops between two companies which can enhance R&D or, in its later stages, distribution. It is prevalent because it allows the expertise of a company to be used in a way that is usually very beneficial. Big pharma will usually licence in research, compounds and/or technology.

Initially, in-licensing seemed to be the obvious route towards securing product pipelines, more so than turning towards collaborations. This way, the model of closed innovation could in some ways, still operate. However, in-licensing has initiated the way towards an open innovation model as the leading pharmaceuticals began to reap the rewards by engaging in licensing deals and subsequently, collaborations. As Rupert Osborn, chief executive and principle consultant from IP Pragmatics points out, "In a lot of other markets, licensing is simply a choice, but in the pharmaceutical industry, it's become a necessity."

"Accessing high quality external and innovative products remains fundamental to our future success and we remain committed to increasing the value of our internal portfolio by acquisition and in-licensing, as well as through our own R&D efforts, commented a spokesperson from AstraZeneca. "Successful companies in this industry will all have one thing in common, an ability to collaborate effectively."

"When big pharma looks to in-licence an aspect of IP relevant to their therapeutic areas,

the trend has been to pick up leads in the later stages of drug development," said Osborn – ideally, post Phase II and Phase III of clinical trials. This way, the risks of subsequent failure in development are easier to quantify than with early stage leads and they can fill holes in their downstream development pipelines. "There are increasingly more opportunities at the later stages of development as biotech companies in particular generate significant discoveries in a range of therapeutic areas. Leading pharmaceutical companies are often inundated with early stage in-licensing opportunities and for them, they can afford to be choosy," said Osborn. "However, smaller companies, for example, biotech companies, often find that they have to do a deal and, it's rare they have a choice of partner."

Erin Brady, healthcare analyst at Datamonitor also suggests that "more late stage deals have been done recently as big pharma seeks near term revenues to stem losses from patent expiries." A recent example of this would be AstraZeneca's partnership with Rigel. AstraZeneca has entered into an exclusive worldwide licence agreement for the global development and commercialisation of fostamatinib disodium (R788), Rigel's late-stage investigational product for rheumatoid arthritis (RA) and additional indications.

Increasingly more and more in-licensing deals are performed by leading pharmaceutical companies. "We do somewhere between 1 and 1.5% of medical research within our walls. That means there's a lot outside to access," said a spokesperson from AstraZeneca. "We want to work with the best academics, the best universities and the best biotech companies to make sure that we really are accessing all that skill and talent." It was reported that between 2008-9, AstraZeneca was involved in 38 licensing deals, making it the fourth most active pharmaceutical to pursue in-licensing agreements behind other big players such as GSK, Pfizer and Sanofi-Aventis[1].

Implications for IP

Opinions on what the implications are for IP are mixed. For some, IP can be the most contentious element of a licensing deal, whereas big pharma defends the notion that it isn't, as all possible scenarios, including contentious ones, are drawn up right at the beginning. "A licensing agreement, above all, must always be a win-win situation for both parties involved," commented Osborn. A full scale valuation of IP is usually carried out so that all the assets are on the table during the negotiation period.

The sellers of the IP need to know what they're willing to accept and what they're not as the buyers will usually have a very clear view on what they will and won't pay. "This can be an area which signals the most contention as in the past, universities and biotech companies haven't always been as equipped with handling IP assets as well as big pharma," said Osborn. "In saying that, with all the licensing agreements and collaborations that are now happening, these centres of innovation are certainly becoming more pragmatic about how they value and assess the IP they are licensing out."

Licensing opportunities, both in and out, create opportunities for IP which has been acquired through innovative R&D, but is unable to move forward without the help of externalisation. Although this helps in advancing things scientifically, it is also extremely costly to harbour unused IP. As big pharma opens up further to adhere to the open innovation model which is becoming more and more advantageous in terms of ground breaking drug development, risk share and knowhow; out-licensing is still a tricky concept. "There are two parts of the idea of open innovation and one is supplementing their own R&D with things they bring in from the outside – a far easier concept for big pharma to get its head around than the second part which is out-licensing," observed Osborn. "The out-licensing of non-core IP assets which all companies will have, sometimes in abundance, is a difficult concept to come to terms with," he continued. "Often they are out-licensing to their competitors and although that IP might not be non-core today, they don't necessarily know that it isn't something they might need again."

In order to discover and innovate in science, it is essential for AstraZeneca to work in collaboration with external organisations to harness emerging science techniques and expertise.

Source: AstraZeneca

Working together

Although later stage in-licensing is still a significant part of the drug development process, especially in a commercial context as pharmaceuticals look to bring a drug to market, early R&D, although scaled back, remains an important focus.

"We're not reducing our focus on R&D, we remain an innovation-focused organisation which we believe will deliver the most value for patients and for shareholders," commented a spokesperson from AstraZeneca. "External collaborations and partnerships are a key to our strategy, allowing us to access the best science regardless of source."

GSK's Skingle reflects that collaborating has been going on for a long time and has increased with the recognition that it is impossible for pharma to do all the research needed with the staff and resources available internally – "scientific advances don't work in this way.

"A main driver for GSK, above all else, is to have access to world class science," said Skingle. "Leading edge and unique science is what drives the results and we must ensure that we embed the outcome of the research into our internal R&D efforts for the long-term benefit of the company and our shareholders."

But why collaborate? "Essentially, the reasons for negotiating a collaboration deal are similar to why big pharma chooses to in-license," said Osborn. "They are to scientifically develop, participate in risk share, to operate cost effectively, but also to get things done quicker." Sir Philip Cohen, MRC Protein Phosphorylation Unit, at Dundee University, says that because "we make so many agents much more quickly and less expensively, some pharmaceutical companies have ended up downsizing or closing some of their in-house teams."

There is little dispute amongst big pharma about the importance to drug discovery of basic research in universities or in the public-sector research institutions (PSRI), as they are also known in the US. In a recent report, which was led by Dr Ashley J Stevens[2], called *The Role of Public-Sector Research in the Discovery of Drugs and Vaccines*[3], it showed that over the past 40 years, 153 new Food and Drug Administrative (FDA)-approved drugs, vaccines, or new indications for existing drugs were discovered through research carried out in PSRIs.

But a criterion has to be met for both parties involved in the collaboration. "For both parties to be happy, the deal obviously has to create value on both sides of the transaction, deliver

therapeutic innovation in areas of unmet medical need, and achieve a healthy commercial return," said Brady. "For this to happen, both sides must be committed to the successful development of the product and both sides must feel the deal terms are fair and reasonable."

Big pharma looks at collaborating as the way forward and the way forward is transparency. "We are externalising more as we reorganise and realign some of our business," said Skingle. "We don't have a monopoly on all of the good scientific ideas and GSK are overt and transparent about attempting to engage world-class academic scientists to drive our internal R&D efforts."

Leading pharmaceuticals are looking right up the chain when it comes down to who they collaborate with and, as Skingle puts it, the concept is becoming increasingly more fashionable. "But the deal needs to be right," he affirms. Skingle points out that there are cases when licensing opportunities are not appropriate and that an intellectual collaboration would be more proactive and constructive. "It doesn't always work simply waiting for that Phase III drug and it's not always about the money…we don't access academia to save money, we access academia to get access to diverse ideas."

Collaborations have proved to be a successful and a scientifically fruitful way to go. Consortiums have become a very popular route to go down, with pharmaceuticals really pulling together to participate more in open innovation to achieve maximum results with academia. A world-renowned and very successful consortium is The Dundee Kinase Consortium, which has been running since 1998. The heart of the consortium is at the University of Dundee and many of the big players in the pharmaceutical industry have dipped in and out of this pool of competitive science.

Implications for IP

So, where does the invaluable IP that makes this all possible come into this? The short answer is that it underpins it, but perhaps surprisingly, is not always a strong area of contention as once the initial contract is drawn up, infringement of any degree becomes quite difficult to implement due to the legal binding of the contract, but this isn't to say it doesn't exist. "When negotiating, it is important to address the most difficult issues first: namely the timing of the expected scientific deliverables, IP control and project costs," says Skingle; and no two deals are the same.

Both the UK and US use specific frameworks to orchestrate a collaboration agreement. In the UK, the Lambert Agreements are referred to when cementing the right deal. There are five model Research Collaboration Agreements, covering one-to-one projects each providing a different approach in the key area of who is to own, and have the right to exploit IP in the results or outcome of the collaborative project; and the four Lambert Consortium Agreements which use the same structure and terminology as the latter, but contain additional provisions to cover some of the complications that arise as a result of having more than two parties[4].

The US is slightly different. "In 1980, Congress passed two pieces of legislation that transformed the ownership, management, and transfer of intellectual property that is created by PSRIs…The Bayh-Dole Act allowed universities, non-profit research institutes, and teaching hospitals to own the intellectual property resulting from federally funded research and to license it according to terms of their choosing" (Stevens et al. 2011 p537).

The key difference between the UK and US is the legality of the framework. "In the US, universities use their statutes to insist on ownership of IP in collaborations. The beauty of this is that it takes away some key areas of contention in a negotiation because the companies know where they stand," said Osborn. "However, if you were to ask big pharma, I imagine that they prefer the UK system because it's more flexible and there is no set framework under which the universities have to act. But, the more flexible something is, the more there is to negotiate over."

Again, it is important to note that academia has become considerably more pragmatic about the way they handle IP in collaborative deals, and do retain a considerable level of academic freedom in terms of publishing results. The Lambert Agreement has certainly provided a successful working model that diminishes the grounds for contention.

It also seems to work within the consortia. One would have thought that having a number of companies working in a single consortium, with all that IP floating around would certainly cause problems, but as Cohen says, "It's a simple model: the companies share what we produce, but they don't share what they produce individually.

"The companies that are in this consortium will share all our unpublished results and ideas, all of our compounds, technology, knowhow and have first rights to license our IP," Cohen said. He adds, "Anything that any individual company shares with us with the purpose of us finding out things they want to know, that information goes back to the one company and subsequently the IP." This is because the university has discovered things for the company which is specific to the company's lead compounds – their own, protected IP. The other side of this is that the university will usually retain the IP when it discovers novel research ideas.

How well does this work? Big pharma has been doing this for a while now, and the concept of open innovation is no longer a restricting one. "It seems to work pretty well, and it works better and better the longer collaboration goes on because trust is created," commented Cohen.

The shape of things to come

In the future, it is likely that internal R&D will not be as extensive as it has previously been for a few important reasons. The cost and the necessity of filling gaping holes in product portfolios are key, but perhaps most importantly, the science that can be accessed outside of big pharma's walls is invaluable and highly progressive. However, it is unlikely that big pharma would ever abandon its entire internal R&D model.

Unfortunately, these efforts from big pharma won't be able to do much about the increasing threat of generic drug companies taking over commercial revenues as blockbuster patents expire. But, on the other hand, they are actively on the right path towards next generation drugs which will keep them at the top of the pharmaceutical chain. Big pharma appears to have established a strategy which is moving with the changing landscape as opposed to against it.

Although externalisation has perhaps limited the control that big pharma will have over its IP assets, the model of open innovation will drive big pharma forward. Open research has become the most fruitful ground on which to work from and the competition is healthy. Big pharma's doors are open for business!

Footnotes

1. *In-licensing deals performed by the top 10 pharma companies by category, 2008-9* Source: Datamonitor adapted from MedTRACK, Deals and Alliances, 4 January 2010, Copyright Datamonitor
2. Director, Office of Technology Transfer, Community Technology Fund, Boston University
3. Stevens, A J. et al. (2011), 'The Role of Public-Sector Research in the Discovery of Drugs and Vaccines', >*The New England Journal of Medicine* vol 364, no. 6, pp. 535-541
4. Intellectual Property Office, *IP, Collaborative Research & Model* in UK http://www.ipo.gov.uk/whyuse/research/lambert.htm accessed on 18 March 2011

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