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Business Development & Licensing Journal

For the Pharmaceutical Licensing Groups

Brexit - Stay or Go?
The EU Life Sciences debate

Introduction & Emergence of Immuno-oncology

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Welcome

Moving deeper into 2016, the UK is facing an interesting summer with the forthcoming referendum in June to decide whether the UK should remain part of the European Union or separate after some 43 years of partnership. Naturally there have been strong views expressed on both sides of the political spectrum focusing on what the economic position might be post Brexit. Certainly it would be an uncertain landscape with so many changes that would impact the industry in terms of IP and regulatory to say the least. So it is no surprise that this issue includes an article from Pinsent Masons reviewing some of the key aspects of the ongoing debate. Later in the year the US presidential election may also bring some surprises that result in significant economic consequences for the pharmaceutical industry.

Other articles in this issue include the feedback from the survey undertaken at the last IPLS conference in Berlin by Roger Davies and Klaus Maleck into financial deal terms. One of the results was the sales multiple that companies are prepared to pay to acquire products. This would be of interest to the delegates at the conference on Business Development and Innovation Opportunities in Consumer Healthcare / OTC. In the PLG News we capture the most interesting features of the presentations from Big Pharma and smaller OTC companies. At the other end of the pharmaceutical spectrum from OTC and one of the hottest therapy areas for deals is immuno-oncology and Chris Sheldon provides an overview.

It will be interesting to see if the political uncertainty during this year has any effect on the number of licensing and acquisition deals.

Sharon Finch

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Should we stay or should we go?

The EU and life sciences - behind the sound bites

Barely a day goes by without a new business figure giving their view on whether the United Kingdom (UK) should remain or leave the European Union (EU). However, what is not clear from all the rhetoric is what the UK's relationship with the EU and the wider world would look like if there is a vote to leave. That said, if the UK votes to stay, the concessions negotiated in February 2016 will have to be implemented and the UK's relationships within the EU and ability to negotiate further derogations may well be damaged. The people of the UK will go to the polls on 23 June to decide whether or not the UK should remain part of the EU. The question will be:

"Should the United Kingdom remain a member of the European Union or leave the European Union?"

By Helen Cline,
Legal Director, Pinsent Masons

About the Author

Helen Cline has a background in genetics and over twenty years' experience of advising clients, particularly in the life sciences sector, on a broad range of IP and regulatory issues. She has a sophisticated understanding of the legal nuances at the interface between patent, medical regulatory and competition law, and, with colleagues from across the life sciences team, aims to deliver innovative patent litigation and regulatory strategies and commercialisation schemes that complement the goals of clients. Helen regularly publishes articles on a broad range of issues. She is on the editorial board of Bioscience Law Review.

The impact of a vote to leave on the UK's life sciences sector is unlikely to loom large in most people's decision on how to vote on 23 June. However, while the EU plays a limited role regulating healthcare itself – each member state retains responsibility for defining its own health policy, organising, delivering and managing health services as well as allocating resources to its health systems – many of the research networks, regulatory systems, funding bodies and forums for discussion are under the European flag. In addition, even if the UK were to vote to leave, decisions made in the EU would continue to have a profound effect on the UK and on life sciences businesses operating out of the UK; the UK, however, could lose its voice and its ability to influence legislation and regulatory developments in the EU.

The issues for the sector are far more complex than the sound bites suggest. Although it would seem that most businesses operating in the sector believe that remaining in the EU is their best option the rhetoric from both sides of the debate is short on facts and there are many unanswered questions.

What is needed is a more honest debate. In terms of the life sciences sector the key issue for most voters will be the impact of the referendum result on their ability to access the best medical treatments and technologies. What is not clear from the headlines is that this decision is, at least in part, one made nationally.

Given the claims and counter-claims about the pros and cons of leaving, or remaining in the EU, this article aims to get behind the sound bites to identify the real issues, as well as risks and opportunities and unanswered questions on both sides of the debate. It will also put the upcoming referendum in its historical context. This article is not promoting one view or the other but aims to be an unbiased assessment of the facts.

Background

Why is the UK having a referendum?

The United Kingdom joined the European Community on 1 January 1973, and confirmed that decision in a UK-wide referendum in 1975. At this time the EU was known as the European Common Market (the inset box has a historic explanation of the EU and an explanation of the terminology). The EU is now far more than a common market and its critics argue that its scope and purpose have shifted significantly since 1975 in ways that nobody predicted. Although supportive of the EU single market, the UK does not support closer political and economic integration. This view is in sharp contrast to the vision of many other EU member states, including France and Germany; they view the EU's single market as a stepping stone toward deeper integration.

Prime Minster David Cameron, in his Bloomberg speech in 2013, agreed to negotiate more favourable arrangements for continuing UK membership of the EU, and to follow these negotiations with a referendum on whether the UK should remain in or leave the EU, if the Conservatives won a parliamentary majority at the 2015 general election, which they did.

What happens if we go?

If the UK votes to leave the EU on 23 June, the secession process will be triggered and the UK is required to notify the European Council of its intention to leave. Withdrawal would not be immediate. There would be a period of renegotiation to determine the UK's future relationship with the EU. During the renegotiation process the UK would continue to operate as a full member state of the EU.

The EU – what you need to know

EEC, EC and EU
The European Economic Community (EEC) was established in 1957. The Maastricht Treaty, ratified by the UK in 1993, established the European Union (EU). One of the pillars of this new Union, the EEC, was renamed the European Community (EC). The three pillar structure established by Maastricht became one, and the European Union replaced the EC, on the entry into force of the Lisbon Treaty in 2009.

The Internal Market
In 1986, the Single European Act was intended to provide new momentum for the establishment of the common market now called the 'internal market' or single market. The internal market, arguably the bedrock of the European Union, is an area without internal borders designed to ensure the free movement of goods, services, capital and persons: the so-called "Fundamental Freedoms".

The member states of the EU
The EU has gone through a period of expansion and currently comprises 28 Member States. Seven rounds of enlargement of the original community of six member states have taken place so far with possible further expansion in the future to include: Albania, the former Yugoslav Republic of Macedonia, Montenegro, Serbia, Turkey, Bosnia and Herzegovina, and Kosovo.

The European Treaties
The Lisbon Treaty amended the Treaty on European Union ('TEU', also known as the Maastricht Treaty), and the Treaty establishing the European Community (also called the Treaty of Rome) and renamed the Treaty of Rome, the Treaty on the Functioning of the European Union ('TFEU').

EFTA
The European Free Trade Association (EFTA) is an intergovernmental organisation set up for the promotion of free trade and economic integration to the benefit of its four remaining member states – Norway, Iceland, Switzerland and Liechtenstein. A country joining EFTA is not automatically a member of the European Economic Area (EEA).

The EEA
The Internal Market is open to the 28 EU member states and three of the four remaining member states of EFTA (Norway, Iceland and Liechtenstein) creating together the EEA. Although the fourth EFTA member state, Switzerland, is not a signatory to the EEA Agreement, it benefits from a number of bilateral cooperation agreements with the EU. Currently, membership of the EEA is only open to EU and EFTA member states and a country joining the EU must apply to be a party to the EEA Agreement. The EEA Agreement provides for the inclusion of EU legislation concerning the Fundamental Freedoms throughout the EEA member states, as well as competition and state aid rules.

EU LAW
EU law is derived from primary legislation (the Treaties) and secondary legislation (such as regulations and directives). It is supplemented by the case law of the European courts (the General Court and the Court of Justice) and general principles of EU law applied by the courts – such as proportionality, legal certainty and subsidiary – as well as fundamental rights which are increasingly part of primary law. EU law confers either directly or upon implementation into national law rights and obligations in each member state, as well as on individuals and businesses. The European Communities Act 1972, as amended, provides the mechanism whereby EU law is incorporated into the domestic law of the UK and enables the implementation of changes to UK law. In case of a conflict between EU law and national law, EU law has primacy.

There are many possible alternative outcomes. However if the UK wished to retain any of the key elements of the single market - free movement of persons, goods, services or capital - it would have to choose a model of integration without membership of the EU such as that enjoyed by the European Free Trade Association (EFTA) countries. The European Economic Area (EEA) agreement and the Swiss bilateral agreements may serve as blueprints for these negotiations. Whatever route were chosen, the UK would no doubt seek to retain some of the benefits it enjoys as a member of the EEA.

The UK government could give effect to its withdrawal from the EU by passing an Act (the Exit Act) repealing the European Communities Act 1972.

The Treaties and all existing directly applicable EU law would cease to apply to the UK from the date the withdrawal arrangements entered into force or, failing that, within two years after notification unless the member states and the UK unanimously agreed to extend this period.

A significant amount of UK law pertaining to the life sciences sector is derived from EU law, either through EU regulations or by way of EU directives which the UK government has itself implemented. At this point it seems unlikely that the UK would seek to repeal all legislation with roots in the EU. It is anticipated that transitional provisions would be included to ensure that all UK regulations made under the 1972 Act and all directly effective EU regulations extant at the time of the Exit Act remained in force, unless and until revoked or amended.

EU regulations could be deemed to be UK regulations made under the Exit Act, effectively repatriating them.

Having said that, it should be recognised that in the event of a 'leave' vote there could be considerable pressure on the UK Government immediately to repeal some aspects of EU law that have been identified as problematic or as giving the UK a competitive advantage.

What happens if we stay?

A vote to stay, if close, it might be suggested could amount to a form of Brexit - a mini-Brexit. As a consequence of the concessions announced by Prime Minister David Cameron, on 12 February 2016, a vote to stay will mean that the UK will retain all its existing opt-outs. The UK will acquire 'special status' within the EU which would in effect exempt the UK from any closer integration. A revision to the treaties will be required to accommodate this concession. What this and the other concessions negotiated will actually mean in practice is unclear but the consensus is that they don't mean much.

If there is a clear majority in favour of the UK remaining in the EU, it is possible that there could be demands for more centralisation and greater political union. The 'leave' camp argue that a stay vote is a vote to acquiesce to future EU demands. If the EU asks for an increased budget, will the UK's 'special status' mean that it is in a position to say no? Does the renegotiation give us an opt-out? How will the planned future enlargement of the EU impact on the UK? Would the UK have a veto?

> "Arguments on both side of the debate … suffer from the same problem: they are highly uncertain predictions"

> “Issues for the life sciences sector are more complex than the sound bites suggest”

The EU and the Life Sciences Sector

“Our health and wealth would benefit from staying in the EU”

Sir Andrew Witty CEO GSK and ninety-two other life sciences leaders in a letter to the Observer 8 May 2016

Given that life sciences companies operate in one of Europe's most regulated sectors, the possibility of a UK exit from the EU throws up a host of industry-specific factors to consider. As is evident from the headline grabbing sound bites from industry leaders and from the evidence given to the recent House of Lords Science and Technology Committee inquiry on the relationship between EU membership and UK science and the ongoing inquiry on EU regulation of life sciences, organisations within the sector are, in general, in favour of continued EU membership. However, there are arguments on both sides of the debate that are worth addressing.

The EU legislative and regulatory framework

.."rules like the EU Clinical Trials Directive have slowed down the creation of new drugs to cure terrible diseases".

Michael Gove’s announcement to join the leave campaign, February 20 2016

The EU's Clinical Trials Directive has been held up as representative of the EU's failings and one reason why Britain would be better off outside the EU. However with new legislation already agreed and a raft of other considerations in play, does this claim hold up?

Although compliance with the complex system of regulation of research and clinical development can be a significant burden, and criticism of EU regulation in areas such as clinical trials is justified, the benefit of a harmonised EU regulatory framework that has taken decades to achieve is important to the sector. In a departure scenario, the question would arise as to what would replace the current system? In the area of clinical trials there is a risk that a period of hiatus may follow, in which companies and funders may be reluctant to invest in clinical development work in the UK (or even manufacture, distribute and market) on the basis that the regulatory system may be in flux and even that a new system, albeit theoretically simpler, may not be as reliable and tested as pan-European regimes. The costs of drug development make it unlikely that companies would take a gamble on new UK regulation being deemed of a sufficient standard by other regulators such as the FDA. Living through a period in which life sciences activity was relocated from the UK to other EU jurisdictions as a risk management strategy could be damaging.

Other arguments for the UK leaving the EU include complaints about ever-tightening regulation. However, companies would have to comply with EU regulations to continue selling into the EU trading bloc.

There are also examples where the EU takes the lead and is taking steps to simplify and take advantage of existing flexibilities in the regulatory and legislative framework, such as adaptive licensing and the Priority Medicines Scheme (PRIME).

It is also claimed that EU legislative processes can lock the EU and member states into a particular policy approach or technological solution that does not easily allow the impact of subsequent policy innovation, new scientific evidence or developments in technology to be reflected. EU legislation can take significant time to negotiate given the need for the agreement of a qualified majority of member states in most cases. Once legislation has been adopted it can be difficult and time-consuming to subsequently amend or repeal. On the positive side, however, there are already signs of change within the EU. There is evidence that the EU is open to adopting a more flexible approach to policymaking. A move to using guidance to interpret legislation is helpful. The EU is also recognising that member states often have different perspectives and legacy health services and sometimes require the ability to tailor policies according to their own economic, cultural and political circumstances. For example, EU member states have recently been given greater power and discretion over whether to allow or prohibit cultivation of genetically modified organisms (GMO). However, there are downsides to this approach. The GMO derogation was a compromise - handing the decision back to member states comes at a price, exclusion from the single market. Many of these issues are also not unique to the EU.

Indeed there are diverging views on GMOs even within the UK with those of Scotland, Northern Ireland and Wales differing from the English perspective.

Another criticism is the lack of engagement early in the EU legislative process with scientific advice and expertise. Whilst acknowledging the new EC Scientific Advice Mechanism, evidence given to the EU Regulation of the Life Sciences Inquiry identified this as one area where there is the greatest scope for improvement within the EU. Examples of policy areas where there has not been enough engagement early on are the clinical trials and data protection regulations.

The convergence of sectors and technologies in areas such as digital health is also challenging existing EU regulatory silos and there is a need for a more flexible approach. However it is unlikely that the UK's ability to tackle this would be any better outside the EU. As previously discussed, the downside to any go-it-alone policies, is that there is the consequential loss of the single market.

Many in the 'remain' camp argue that if the UK leaves the EU, no alternative to full membership will give the UK the ability to influence the direction of EU regulation and legislation. That may be true, but it seems pertinent that the UK is the most out-voted member state in the EU Council.

Funding

Outside the EU there is the possibility that the UK would have reduced access to EU funding and much reduced influence on the strategic direction of the various EU schemes.

UK life sciences organisations have benefited substantially from their ability to participate in grant funding schemes administered by the EC such as the Framework 7 programme and the current Horizon 2020 programme as well as the European Investment Fund. As well as access to considerable funding, there has been the more intangible, but still significant benefit, of participation in arrangements through the Innovative Medicine Initiative that often facilitate collaboration between organisations across Europe, both academic and public sector research institutions and private sector companies. This has led to some valuable outputs and knowledge sharing. There are concerns that the UK outside the EU risks losing the right of UK organisations to participate in such programmes. However, it is arguable that leaving the EU and possible relief from obligations to pay contributions to the EU budget could make more money available for the direct funding of UK R&D. However it is by no means certain that such funds would be used to fill any gaps in R&D funding.

"UK life sciences organisations have benefited substantially from their ability to participate in grant funding schemes"

Access to these collaborative programmes is possible from outside the EU. Switzerland, a member of EFTA, has engaged in them as an external participant. However, broad compliance with EU principles is necessary to get access to funding and collaboration through programmes such as Horizon 2020. A vote to leave the EU is likely to harden UK government policy on immigration. This may make it difficult to win political support in the UK for the freedom of movement terms that are required to secure associate status for access to EU research networks.

Licensing deals

Life sciences organisations also currently benefit from the stability of EU laws and regulations which govern research and technology licensing such as the R&D block exemption and the technology transfer block exemption. The provisions of these exemptions have been in place for some years and provide a general position which allows for contracting on a familiar and fair basis, restricting unfair terms such as a requirement for a licensee of a patent to be compelled to assign any improvements to the patent owner. Whether these provisions would continue to apply will depend on the terms of the renegotiation. If the UK was outside of European competition regulation it is uncertain what elements of these provisions the UK would retain and which may be replaced altogether. During the negotiation process the UK could seek to limit the uncertainty by repatriating the exemptions into UK law.

> “..it is not possible to say definitively the extent to which membership of the EU is a factor in inward investment decisions”

Investment

Establishment in the EU gives companies access to a single market of some 500 million people, with a combined GDP of £11 trillion, in which companies can freely trade. While it is not possible to say definitively the extent to which membership of the EU is a factor in inward investment decisions, it is undoubtedly a factor. Many non-EU firms regard the UK as the way into the EU market. How would an exit from the EU and any renegotiation impact these flows? In the period of uncertainty during any renegotiation of the UK’s relationship with the EU there is a risk that foreign companies could divert or postpone investment into the UK. However if the UK government continues to deliver on its strategy for the sector and puts in place measures to encourage continued inward investment such as tax incentives and reliefs there is no reason why in the longer term inward investment would not fully recover and even increase.

Trade and global markets

The EU facilitates global trade by providing access to over 50 markets outside the EU through trade deals. Although both the EU and member states are members of World Trade Organisation (WTO) in their own right, in practice, within the WTO the EU speaks on behalf of both the EU and the member states.

> EU membership is a precondition for participation in the new unitary patent system

The EU has successfully negotiated a free trade treaty with South Korea and there are ongoing negotiations for a controversial agreement to abolish all business tariffs between EU and US.

No alternative arrangements to full membership of the EU will provide UK businesses with access to the free trade arrangements the EU has in place with third countries. Many of these free trade agreements, as well as removing tariffs, mutually recognise products approved under similar and equivalent regulatory systems. Post an EU exit unless the UK joined EFTA and could benefit from its trade agreements, the UK might find itself having to renegotiate trade agreements with over 50 countries. A UK outside the EU would be able to negotiate new deals but would the UK's negotiating power be the same as the EU's and would it be able to contract on the same terms as the EU?

Also, will negotiating a trade deal with the UK be a priority for these countries? It could be that the UK's negotiating power is weakened and it may find itself under pressure to open up its markets without full reciprocal access. That said, there are disadvantages in the current arrangements. The interests of all 28 member states have to be considered.

The protracted negotiations and differences of opinion recently exemplified by the Dutch referendum on the EU's agreement with Ukraine highlight the downside of the EU's exclusive competence over trade and commercial policy.

Patents

In terms of patent registration and enforcement in the UK as currently practised an exit from the EU and the consequential renegotiations would have little impact. With a few exceptions, patent law is not harmonised across the EU. It is defined by national law and international treaties such as the European Patent Convention (EPC).

However EU membership is a precondition for participation in the new unitary patent system: if the UK is no longer an EU member state, unitary patents would not have effect in the UK and the UK could not be party to the Unified Patent Court (UPC) Agreement. The UPC aims to facilitate more consistent decisions in patent litigation. If the UK were no longer in the EU, patent protection for inventions in the UK would be obtained (as now) by either validating European patents upon grant to have effect in the UK, or by filing nationally through the UKIPO or under the auspices of the Patent Cooperation Treaty (PCT).

> “Having a harmonised and level playing field is of course a bonus”

The UK is currently the leading venue for life sciences patent litigation in the EU with a wealth of relevant expertise. The life sciences seat of the central division of the UPC is currently located in London. This does not seem to be dependent on the UK being part of the unitary patent system (or indeed a member state of the EU). However, if the UK was no longer able to participate in the unitary patent system, it is likely that this London-based seat of the central division would be moved to another member state.

One area of patent harmonisation in the EU is the Biotechnology Directive. There have been calls for the UK to withdraw from EU jurisdiction in biosciences to escape what has been termed "anti-science" politics in Europe. The Biotechnology Directive and decisions around patentability are seen to be undermining confidence in the EU commitment to create a favourable place for life sciences companies to do business. However, even within the UK opinions on the availability of patents in the field of biotechnology remain divided and an EU exit is unlikely to resolve this issue.

Data

It is possible that smarter policy making to support the use of big data analytics in the UK in medical research might arise if the UK votes to leave. However, any changes to UK data privacy rules that do not accord with EU law could jeopardise investment in the UK.

Changes will be made to the UK's data protection framework regardless of which way the vote goes. If the UK votes to remain in the EU then the EU General Data Protection Regulation would apply to businesses operating in the UK or targeting UK-based consumers. If the UK votes to leave the EU then there is considerably more uncertainty over UK data privacy rules.

As it is not yet clear what the nature of the UK's relationship with the EU would be post-exit, the new General Data Protection Regulation could either apply in the UK or at least heavily influence how a post-exit UK data protection regime would look. Life sciences organisations want consistent data privacy rules across national borders in Europe and might think twice about laying foundations in the UK if using UK data centres would not give them an automatic right to transfer data across the whole of the EU.

Other considerations

Other considerations that have not been touched on in this article include workforce, taxation and competition law. However, nobody is suggesting, whatever the outcome, that borders would be closed to scientists, engineers or professionals. The evidence is that countries with immigration systems based on strict point’s quotas, such as Australia, ensure free flow of skilled professionals.

> UK is often seen as the driver of change and a moderator of more extreme views.

The impact of a future UK exit from the EU on the devolution settlement should also be considered. Would a UK exit from the EU trigger a new referendum on Scottish independence or calls for further devolution from other UK nations? What would be the implications if an independent Scotland voted to remain in or rejoin the EU?

Is life outside the EU incompatible with a thriving life-sciences sector?

'the choice in this referendum: our economic security and global influence as part of the EU, or a leap in the dark.'
Life Sciences Minister George Freeman MP in response to letter to the Observer 8 May 2016

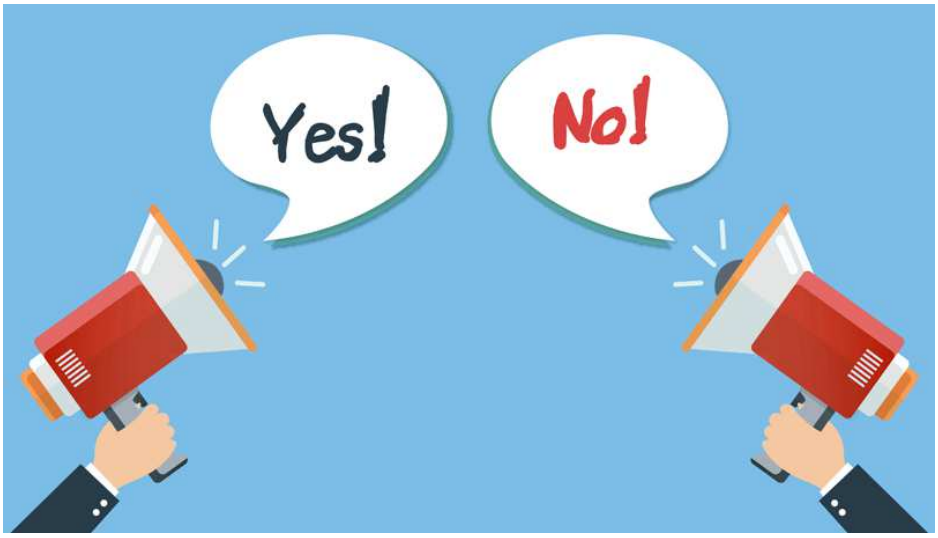
Is the success of Switzerland's pharmaceutical industry evidence that life outside the EU is not incompatible with a thriving life-sciences sector?

As the centralised procedure and incentives such as orphan designation would no longer apply to the UK, some arrangement with the EMA would be important. Assuming some agreement could be reached quickly during the negotiation period when the UK would still be a member of the EU any disruption could be minimised. The UK could perhaps negotiate a Mutual Recognition Agreement similar to Switzerland's.

Switzerland also has a long tradition of cooperation in research and innovation with the EU. Researchers in Switzerland have been participating in the EU Research Framework Programmes since 1988. However, Switzerland's ability to participate was compromised when it adopted stricter immigration policies. As discussed earlier; a vote to leave the EU is likely to harden UK government policy on immigration. This may make it difficult to win political support in the UK for the freedom of movement terms that are required to secure access to EU research networks and funding programmes.

Outside the EU it is arguable that the UK would still be an attractive place for life sciences organisations to do business and invest. Other than our EU membership there are other factors that make the UK attractive including a world class science base; many of the world's top universities; a unique resource of patient data from within the National Health Service (NHS); a supportive taxation regime; and a well established and progressive regulatory regime.

What is difficult to predict is the impact of a vote to leave the EU on these resources. Those in the 'remain' campaign argue that single market access is a key factor in the decision-making process for foreign companies but perhaps this has been over emphasised? No one is suggesting the UK would stop trading if it left the EU. Having a harmonised and level playing field is of course a bonus and reduces costs and paperwork but trade is likely to continue with the EU.



It has also been argued that a vote to leave the EU would mean that medicines would be launched later in the UK. But why not UK-first and not UK-last? If a UK-last approach proves to be an accurate prediction, it seems unlikely that a vote to leave the EU would be the deciding factor. The economic climate in the UK is forcing prices down and many businesses no longer find it viable to innovate and commercialise products here. This is not an issue associated with EU membership.

Although the harmonised regulatory framework and funding and collaborations under the auspices of the EU are important, of equal or perhaps more importance to life science businesses is that systems are in place to ensure the speedy adoption of medical innovations. The EU legislation to fast track innovative drugs, has been underused. Although there are moves in the EU arena to remedy this with adaptive licensing and the PRIME scheme, the UK has launched its own initiative, the Early Access to Medicines scheme. This aims to make medical treatments that satisfy certain criteria available to patients in the UK before anywhere else in the world.

Pricing and reimbursement decisions remain a national competency. In England reimbursement decisions are made by NICE. Leaving or staying in the EU will not on its face influence these decisions although there are those that argue that if the UK left the EU the UK government would be under pressure to act to preserve investment in the UK's life sciences sector and the regulatory mechanisms already under review as part of the Accelerated Access Review (AAR), including the NICE appraisal process, would be changed. The final report of the AAR has been delayed until after the 23 June, possibly to allow for some last-minute tinkering should the vote be to leave.

Conclusion

Arguments on both sides of the debate that say there will be this cost, or these benefits, to leaving the EU suffer from the same problem: they are highly uncertain predictions. It is only possible at this stage to speculate what kind of deal the UK (or even possibly England on its own) will be able to negotiate not only with the remaining member states of the EU, but also with countries outside the EU.

At the end of the day although many of the sound bites from the 'remain' campaign are about how the UK needs the EU, the reverse is also true.

The UK is often seen as the driver of change and a moderator of more extreme views. An EU without the UK could collapse. The 'leave' campaign point out that EU countries are net importers into the UK and that it is arguable that this would mean that the EU would not put up trade barriers. On the other hand, however, it may be seen to be important to make an example of the UK to ensure that the UK exit does not set a precedent for similar action by other member states. This might be more important to policy makers than the impact tariffs might have on EU companies exporting to the UK. Only a few countries within Europe export a significant amount to the UK and the remaining 27 member states would all have an equal vote in the post Brexit negotiations.

No one knows what will happen on 23 June. Whatever the outcome, the EU will continue to have an impact on the UK and the life sciences sector.

If the people of the UK vote to leave the EU it seems unlikely that this would be a disaster for the UK's life sciences sector as some have suggested. The life sciences sector has been described as the 'jewel in the crown' of the UK economy and it is reasonable to suppose that politicians and civil servants will find a way to limit the damage.

What needs to be done?

The uncertainties surrounding the upcoming referendum and its aftermath are such that there may be a temptation to adopt a wait-and-see approach until the referendum result is known. However, these action points are worth considering:

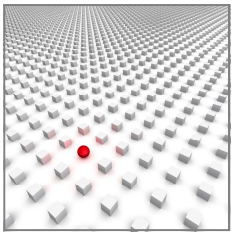
- **Ensure access to information** on progress of renegotiations / implementation of concessions to facilitate appropriate plans in response and consideration of the commercial opportunities.
- **Put in place contingency plans** around the different referendum scenarios that take account of the varying permutations around trade rules, regulations and access to funding. Review and adjust these as more information becomes available.
- **Open dialogue** with clients and subsidiaries in the EU to plan for the possible impact the referendum and any consequential negotiations might have.
- **Review and build flexibility into existing and future contractual arrangements** to protect key contracts and consider how contracts may be affected by different referendum and renegotiation scenarios.
- **Review patent filing and commercialisation strategies** in the light of new patent choices and forums for enforcement under the unitary patent system. The risk-benefit analysis of one choice over another may change in light of the referendum decision.
- **Review product pipeline** and consider how the result of the referendum might affect development and launch plans.
- **Ensure data availability and** consider whether key data is available locally in the UK and/or in EU member states following the referendum.

For more discussion of these issues see our article "Repositioning Deals - Contingency Planning for Possible UK EU Breakaway" published in issue 22 July 2015 of the PLG's Business Development and Licensing Journal.

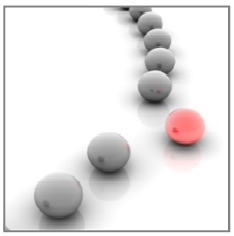
The author would like to acknowledge the assistance of Louise Fullwood in writing this article. The opinions in this article are the author's own.

Healthcare Business Development Training

The PLG UK Ltd provides a range of comprehensive training courses that cover all areas and stages of Healthcare Business Development, from the Introductory course to the MSc. PLG members and group bookings qualify for discounted rates.



Introduction to Healthcare Business Development is a three day training course covering the key elements of Licensing and Business Development. It has a 12 strong faculty providing guidance on best practice using case study material. It also includes a hands-on example of negotiating a deal.

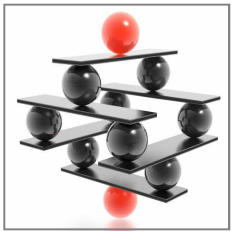


Early Stage Healthcare Training is a new one day training course devised by the PLG to provide a comprehensive overview of Healthcare Business Development fundamentals for those involved in early stage deals.

The Masterclass is an interactive two-day course which provides delegates with practical in-depth analysis and tools for Healthcare Licensing and Business Development.

Continuing Professional Development Single Subjects by Distance Learning

The individual modules which comprise the MSc are available as stand-alone units.



MSc in Pharmaceutical Business Development & Licensing

The Pharmaceutical Licensing Group in conjunction with the University of Manchester runs a modular distance learning course which can result in an award of an MSc in Business Development in the Healthcare industry. This course offers a range of modules which can be studied sequentially to secure a full MSc qualification.

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Introduction & the Emergence of Immuno-oncology

Oncology has always been an active area for research and development in academia, biotech and pharma, however what is unprecedented is the recent volume of deals in this space, fuelled almost entirely by the game-changing area of immuno-oncology (IO).

By Chris Sheldon, AstraZeneca

About the Author

Chris Sheldon has worked in the UK at AstraZeneca for 14 years and is currently Head of Oncology Search & Evaluation in AstraZeneca's Global Product & Portfolio Strategy Team. Chris and his team are responsible for leading the technical evaluation of new M&A, in-licensing, out-licensing (divestment) and collaboration opportunities in clinical stage oncology. Most recently, he led the evaluation of AstraZeneca's recent majority stake investment in Acerta Pharma, as well as multiple novel immuno-oncology combination deals for AstraZeneca's checkpoint inhibitors, durvalumab and tremelimumab.

Rather than targeting the driving factors of cancer directly by interfering with specific molecules that are involved in the growth and progression of certain cancers (targeted therapy), IO is different and acts by targeting a cancer patient's own immune system to help fight and destroy the cancer. IO therapies broadly work by either 'taking the brakes off' the immune system, by inhibiting the so-called 'checkpoints' (proteins that need to be de-activated to start an immune response), or boosting the immune system's ability to detect and destroy tumours – the so-called 'putting the gas on' effect. The first generation IO therapies target the cytotoxic T lymphocyte associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) checkpoint receptors (or the associated ligand PD-L1) and have become standards of care in multiple tumour types such as non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC) and just recently both classical Hodgkin's Lymphoma (cHL) and bladder cancer. Other indications are likely to follow over the next one to two years, where multiple PD-1/PD-L1 agents have the coveted FDA breakthrough designation based on their step change efficacy profiles shown to date.

The first two cancer-fighting PD-1 drugs, Merck & Co's KEYTRUDA (pembrolizumab) and Bristol-Myers Squibb's (BMS) OPDIVO (nivolumab), both hit the market in late 2014 and now just last month TECENTRIQ (atezolizumab) from the Genentech Inc. unit of Roche is notably, the first PD-L1 inhibitor to be approved by the FDA. Others will soon follow, including AstraZeneca/ MedImmune's durvalumab and Pfizer/Merck KGaA's avelumab, both PD-L1 targeted agents. The uptake of OPDIVO in the market has been quite remarkable, already achieving blockbuster status in the handful of indications where it is approved; with BMS slating quarter one 2016 sales of $704m and therefore expected global sales for the whole of 2016 in excess of $3bn.

'Lifting the tail' – long term 'cures'

The rapid uptake and unprecedented interest in IO lies in the emerging data shown in the Kaplan–Meier graph below (Fig. 1), taken directly from OPDIVO's FDA approved label in 2nd line NSCLC versus the current standard of care in this setting, an old chemotherapy drug, docetaxel.

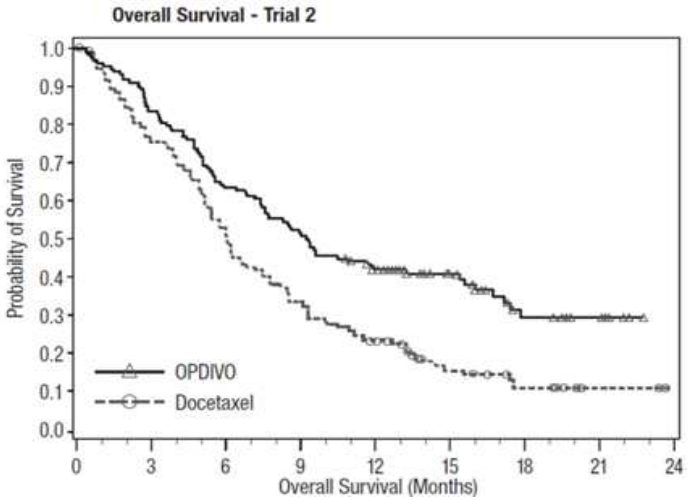
This significant finding, showing that OPDIVO increases both (i) median overall survival (by around three months) and (ii) long term survival after 2+ years for 20-30% of patients, enabled the rapid regulatory review and approval of OPDIVO in 2nd line lung cancer, and since then, many other indications.

Historically, targeted therapies (agents that target a particular genetic abnormality or mutation driving the disease), represented by the yellow line in Fig. 2 below, typically show high response rates leading to enhanced progression free survival and sometimes overall survival vs chemotherapy (grey line). However, resistance mechanisms inevitably cause all patients to experience disease progression and the curves ultimately end up converging. The brand new IO agents, represented by the red line, cause a 'lifting' or 'tailing' of the Kaplan -Meier curve that means that 20-30% of patients have a long term and highly durable response, providing clinical validation of the memory effect that our immune systems have in keeping cancer away. These astonishing findings have even led people to start using the term 'cure', which is unprecedented in the area of oncology based on previously generated data.

Next generation IO – combinations, combinations, combinations

Whilst checkpoint inhibitor monotherapies have resulted in dramatic responses in some individuals, not every person responds, and the responses often are not durable.

Fig. 1 Extract from OPDIVO's label



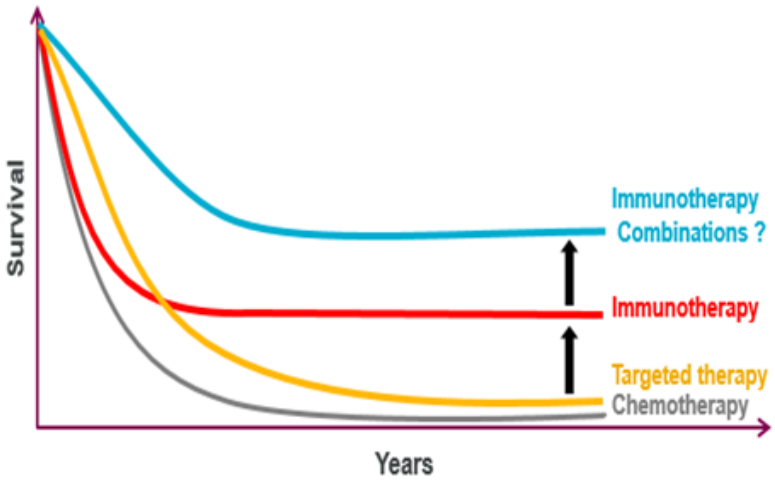
The challenge now rests firmly with next generation combination regimens in an attempt to increase both response rates and the durability of response without substantially increasing side effects. This concept is shown in blue in the graph below (Fig. 2), where the curve is both lifted and shifted significantly out towards the right.

The industry however is faced with a cornucopia of potential combination options as the science around them continues to evolve rapidly.

The number of different tumour types further complicates this, and when overlaid with the different biological hypotheses, makes for a very complex matrix.

Pharmaceutical and biotech companies are therefore being thoughtful about where to make their IO investments. The ultimate strategy is to fill in the entire matrix as far is practically possible, with the aim of allowing all cancer patients to benefit from new, potentially game-changing IO treatments.

Fig. 2 Graphical representation of the future of combinations



> “There is no crystal ball and the jury is firmly still out”

This has created the perfect environment for collaboration and sharing of ideas, and is directly responsible for the high levels of deal-making activity that we are seeing in the industry.

The simple truth however is that no-one knows what the ‘killer’ combinations will be, hence the apparent ‘spread-betting’ seen across the industry, but with each player being very disciplined and focused on rational combinations. A common strategy, for example, involves testing the PD-1/PD-L1 checkpoint inhibitors with a variety of marketed targeted therapies with well-categorised activity, capitalising on the fact that we now know that these immune checkpoints are both safe and efficacious and are therefore sound foundations - or the so-called ‘backbone’ - for combinations.

Following the science – finding the right combinations

At AstraZeneca our decisions are guided by clear, biological hypotheses and strong preclinical data, leveraging internal subject matter expertise.

Whether a combination includes two (or more) IO therapies or IO agents alongside chemotherapy or other targeted oncology medicines is a decision made only with the backing of data and a sound hypothesis. For example, it is common practise to look for preclinical evidence that a combination will trigger an immune response by looking for evidence of CD4+ and CD8+ T-cell modulation/ infiltration.

It is still very early days however and we eagerly await further data. There is no crystal ball and the jury is still firmly out on what the most efficacious combinations might be, given the number of available options. Even older chemotherapies (therapies that do not discriminate in killing healthy versus cancerous cells) may be combined with new IO agents - when cytotoxic chemotherapies kill cancer cells they shed antigen[s] that can then be recognised by an army of T cells (white blood cells) and prompt an immune response, allowing these T cells to infiltrate the tumour and then destroy it. Combining a checkpoint inhibitor with an older chemotherapy could therefore be additive, or even potentially synergistic. BMS, AstraZeneca and Roche are all following this strategy across multiple tumour types.

Bring on the deal making deluge (with no strings attached)

It is no surprise, given their place as a potential backbone of the IO universe, that those companies with marketed or clinical-stage PD-1 or PD-L1 immune checkpoint assets find such agents to be in great partnering demand.

Alongside M&A, licensing, strategic alliances and option deals, so called ‘no -strings-attached’ clinical trial partnerships and collaborations have driven combination-therapy trials in IO. These deals, and there are literally dozens of them, are typically limited to two companies agreeing to test their assets together in the clinic, without significant downstream commitment.

In AstraZeneca's own experience, clinical trial partnerships can take weeks to put in place, rather than months as is common for traditional alliances. The driving force behind this is a simple one: competition. These deals enable companies to rapidly test clinical hypotheses by sharing the risks together.

Preclinical data can be predictive, but rarely perfectly so, hence many companies are adopting a common sense approach to assessing combination therapies by moving directly into the clinical to optimally test a particular hypothesis. As an industry I feel like we are working to ask all the right scientific questions and seeking answers in the most efficient way possible, for the benefit of patients. IO has really brought the industry together and the amount of collaboration is both breathtaking and inspiring to see.

The deal making frenzy all began back in 2014 when Incyte Corporation slated four major pharma alliances in a period of just six months, all focussed on combining its Indoleamine 2,3-Dioxygenase 1(IDO-1) targeted agent (epacadostat) with the PD-1/PD-L1 class - and all with apparently no strings attached or non-exclusive in nature (Fig. 3 below).

Fig. 3 Speed dating in action - IDO combinations with immune checkpoints

PD-1/PD-L1 Agent	Tumour Types	Date announced
Nivolumab (BMS)	Melanoma, non-small cell lung (NSCLC), ovarian, colorectal (CRC), squamous cell carcinoma of the head and neck (SCCHN) and diffuse large B-cell lymphoma (DLBCL)	May 2014
Durvalumab (AstraZeneca)	Metastatic melanoma, NSCLC, SCCHN and pancreatic cancer	May 2014
Pembrolizumab (Merck & Co)	Metastatic and recurrent NSCLC, among other advanced or metastatic cancer	February 2014
Atezolizumab (Roche/Genentech)	Not disclosed	July 2014

Then, just in October last year Incyte and Merck & Co both announced an expansion of their relationship, to take the nivolumab and epacadostat combination into a phase 3 study in melanoma, this time on an exclusive basis for a period of two years, presumably reflecting the significantly higher level of investment in such a pivotal study versus the earlier, and non-exclusive, signal searching efforts previously announced.

AstraZeneca's PD-L1-directed antibody, durvalumab, has also formed the foundations of a broad range of IO deals, such as a strategic alliance with Eli Lilly & Company. This deal will see durvalumab tested in combination with several of Lilly's experimental IO candidates and was announced in May 2015 and subsequently expanded in October 2015 (Fig. 4). This approach at testing multiple combinations is particularly attractive as a number of hypotheses can be tested simultaneously with the added benefit of synergies in doing these efforts in parallel.

Fig. 4: Multiple combinations will be investigated by AstraZeneca and Lilly on a non-exclusive basis

AstraZeneca Agent	Lilly Agent	Tumour Types
Durvalumab (PD-L1)	CSF-1R antibody	Not disclosed
Tremelimumab (CTLA-4)	CSF-1R antibody	Not disclosed
Durvalumab	Galunisertib (TGF-β)	Not disclosed
Durvalumab	CYRAMZA, ramucirumab (VEGFR-2)	Gastric, gastroesophageal, non-small cell lung and hepatocellular cancers
Durvalumab	CXCR-4 peptide antagonist	Not disclosed

Colony stimulating factor 1 receptor (CSF1R)
Transforming growth factor beta (TGF-β)
Vascular endothelial growth factor receptor (VEGFR)
C-X-C chemokine receptor type 4 (CXCR-4)

However not every clinical trial partnership is designed to enable 'dating' multiple partners. For example, in a deal with Pfizer and Merck KGaA that was announced in January, Syndax Pharmaceuticals plans to test its drug, entinostat, a small-molecule histone deacetylase (HDAC) inhibitor, with avelumab (another PD-L1 mAb) in individuals with heavily pre-treated recurrent ovarian cancer. That deal is exclusive with regards to the tumour type, and Syndax will combine entinostat only with avelumab. However Syndax can, and has, combined its HDAC inhibitor with other IO assets, such as Merck & Co's KEYTRUDA, in different indications (this particular combination is being tested in NSCLC and melanoma under a deal made in March 2015).

We patiently await the verdict of the jury

While the jury reaches its verdict and more data become available, we continue to see combinations announced every week. IO is an area of research that lends itself extremely well to partnering based on the data to date, building on the solid foundations laid by the first generation IO agents and attempting to add shelf life to what would otherwise be superseded agents due to this new armamentarium redefining the medical text book.

Such IO combinations, if the right balance of efficacy versus tolerability is reached, could mean fast-to-market strategies and 'leap frogging', reducing the shelf life of other standards of care by many years. The competition is fierce, the data are telling us clearly that combinations are the way forward and therefore I see no reason why - in the near term at least - there will be any slowdown in clinical combinations and the necessary deal making in order to deliver upon them.

Partnering for scientific leadership

AstraZeneca

At AstraZeneca, we believe in the power of what science can do to transform serious diseases like cancer, heart disease, diabetes, COPD and asthma.

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Atlas approval ID: 826,131.011 Expires 05 July 2016

Financial Valuation & Deal Terms in Healthcare Business Development & Licensing Deals

The heart beats faster, the brain works at high speed: The crucial negotiation round is approaching, but are you prepared? Do you have a clear understanding of what you need to achieve and a solid background argumentation? All stakeholders aligned, "all ducks in a row"?

By Klaus Maleck, Tetec AG and Roger Davies, Medius Associates Ltd.

About the Authors

Roger Davies works with Medius as a consultant specialising in valuations, deal structuring and negotiating late stage licensing, commercialisation and M&A deals.

He is the former Chairman of the UK Pharmaceutical Licensing Group, the professional association of licensing and business development executives, and is the Finance module leader for the healthcare Business Development and Licensing MSc at the University of Manchester.

Klaus Maleck is CEO at TETEC AG, a company specialising in regenerative medicines. During his tenure and his function as CFO at several biotech companies, he generated a track record in deal making and M&A. He also worked as a consultant at McKinsey and Co.

He regularly lectures at several universities on finance, valuation and corporate development topics, and is a tutor of the Finance module for the healthcare Business Development and Licensing MSc at the University of Manchester.

'Reasonable' financial deal terms

Then it will be a home run to generate a broad consensus on the overall asset value. The next step is to negotiate 'reasonable' financial deal terms for both parties. What is 'reasonable'? It depends who is asked: the seller or the buyer and their respective negotiators, negotiators' management or Board or investors. So the negotiator may rely on benchmark terms from comparable deals to justify the proposed deal terms as 'reasonable'. The bad news is there are not many comparable third party deals where the full financial deal terms are published, especially royalty rates.

Valuation assumptions, methodology and sharing data

One of the key elements in negotiating a deal is to ensure that both sides have similar expectations about the valuation of the asset and what financial deal terms are 'reasonable'.

The valuation is driven by the assumptions and methodology used in the financial model. For example one of the key financial assumptions is the discount rate (weighted average cost of capital, WACC) used in a net present value model. WACC changes over time as interest rates and equity risk premiums change as for example in the aftermath of a financial crisis. During deal negotiations, differences in valuation between two parties can usually be resolved easier by sharing information about assumptions and/or methodologies.

Survey sources and objectives

Various surveys have been undertaken over the years by consultants and organisations to obtain information about valuation and financial deal terms specifically for the healthcare industry. These surveys tend to be focussed on licensing of speciality pharmaceutical products.

To get a wider perspective, a survey was undertaken by the authors of this article in September 2015 amongst the delegates at the International Pharmaceutical Licensing Symposium (IPLS) in Berlin organised by the European Pharmaceutical Licensing Groups (PLGs) and some other PLG non-attendees. Almost all of the IPLS delegates were business development and licensing executives working in the healthcare industry in Europe in biotechnology, branded speciality medicines, OTC and generics.
The objective of the survey was to obtain opinions from different types of companies on the following:

Valuation methodologies and sharing data

- ◊ Which financial analysis methods are most valuable for different types of deals?
- ◊ What information do licensors and licensees disclose to align expectations?

'Reasonable' deal terms for different types of deals

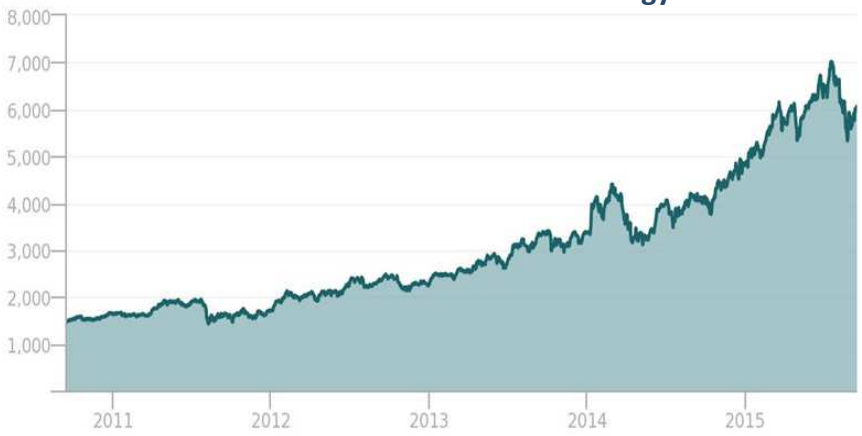
- ◊ Maximum and minimum royalty rates
- ◊ Licensee share of project value
- ◊ Maximum and minimum gross profit margins by company
- ◊ Sales or profit multiples for a product acquisition deal

What type of training do business development executives receive?

The financial environment

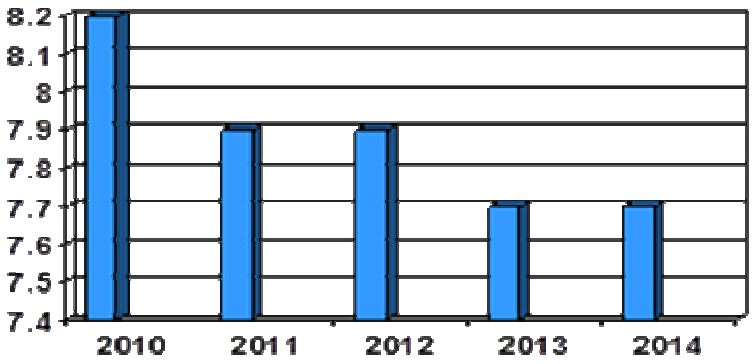
Valuation assumptions are very much determined by the financial environment. In the five years prior to September 2015 there was a steady rise in the value of US biotechnology companies as measured by the S&P share price index.

Chart 1 Standard and Poor's Biotechnology Index



The question is whether there was (i) a fundamental increase in value driven by more projects and full pipelines or (ii) was the increase fully or partly explained by financial reasons or (iii) do we face a blown-up valuation without justifying reasons? According to KPMG, the average cost of capital (%) in the life science industry has decreased but only by 0.5% points in the period 2010 to 2014.

Chart 2 Average cost of capital (%)



This may explain anecdotal information that business development departments in pharmaceutical companies are still using a similar discount rate / weighted average cost of capital (WACC) for Net Present Valuation calculations as was used prior to the financial crisis of 2007/08. Certainly some big pharma companies are using very similar discount rates to the rates in 5+ years ago, e.g. AstraZeneca's post tax WACC for impairment of intangible assets is quoted as 7.6% pre risk adjustment in 2009 and 7.0% for the years 2013-15.

Of course, the WACC is based on long -term assumptions (i.e. interest rates of 30 year government bonds) and does not jump on a daily basis readily following short term-trends. But clearly, in a macroeconomic context, cheap money has not led to an increased spending for R&D. What can be observed is actually that the cheap money does not only not foster innovation, but also might have some detrimental effects on innovative SMEs. While big companies (Gilead, Valeant, Actavis, etc.) have issued their own bonds or tapped into the equity markets, SMEs at times of a closing IPO window and dried-up VC funds, are stuck to the banks which themselves are consequently left with a riskier portfolio. In exchange, banks prefer to invest into low risk investments, such as government bonds rather than investing into productive investments. In addition, cheap money does not fulfil the evolutionary function of selection of the fittest company, leading to a slowed-down innovation cycle.

Without an increase in R&D efficacy, the increase in values of the biotech/ pharma companies observed at the stock and M&A markets are not supported by the underlying facts. This "stretched valuation" (P. Witty) might lead to massive amortisation of intangible assets in the P&L of the many acquiring companies in the industry in a few years. In terms of valuation, the question remains: How can the high values be justified, which assumptions and methods are currently used to derive and justify the terms of acquisitions and licensing deals?

Survey response

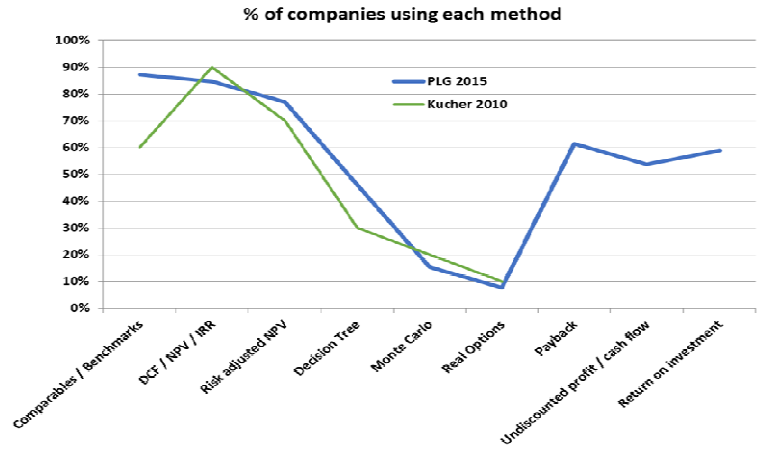
39 responses were received of which 54% were pharma, 33% biotech and drug delivery and 13% generic/OTC/ Medtech. There were 8 large companies, 11 medium and 20 small. The number of responses is too small for statistical significance by type of company but the number of responses provides a good estimate in aggregate and is comparable to the Simon Kucher survey in 2010 (n=40) and the LES survey in 2012 (n=35).

Valuation Methods - "It is better to be roughly right than exactly wrong" (John Maynard Keynes)

In 2010 Simon Kucher presented results of a survey "Trends in In-Licensing and Out-Licensing in the Pharmaceutical and Biotechnology Industry". The results showed the most frequently used valuation methods for licensing deals. As far as we are aware it did not include product acquisition deals or an analysis by stage or type of deal e.g. patent licence, early stage, late stage, co-promotion. The PLG survey also included non-discounted valuation methodologies such as payback and return on investment. The PLG survey produced very similar results to Simon Kucher except there was a higher use of benchmarks for the valuation of deals in the PLG survey. This may have been because the PLG survey included OTC and product acquisitions where benchmarks may be more prevalent.

In summary, more than 80% of companies use benchmarks, net present value (NPV) and risk-adjusted NPV (rNPV) and less than 15% used 'black box' methods such as Monte Carlo and real Options.

Chart 3 Valuation methods used in pharmaceutical deals



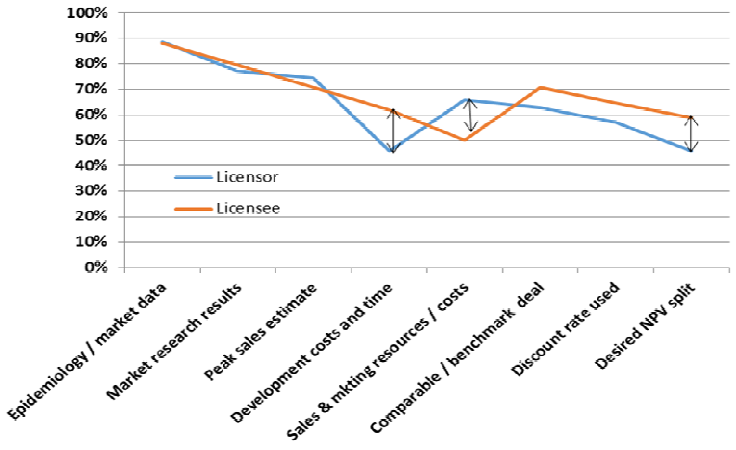
Valuation methods by type of deal

As expected each respondent uses two to three valuation methods to evaluate each type of deal. For example, an early stage (preclinical, phase 1) licensing deal is assessed using benchmarks, NPV and rNPV. A generic deal is assessed using payback, NPV and benchmarks. Some types of deals have products closer to the market and are shorter in duration than others e.g. distribution deals usually have a product in registration and may only have a five year term whereas an early stage licensing deal may be over five years to the market and a ten year or more term. In this situation one would a priori expect the longer term deals with development risk to be more heavily reliant on rNPV than a distribution deal but survey results did not show a marked difference.

However there was a broad consensus that

- For licensing deals, benchmarks, NPV and rNPV are the top valuation methods but
- For deals such as product acquisitions, distribution, OTC and generics, benchmarks, undiscounted cash flow and return on investment (RoI) were the top valuation methods

Chart 4 – Willingness to disclose data to the other side



Aligning expectations - "Successful investing is anticipating the anticipations of others" (John Maynard Keynes)

Aligning expectations is a fundamental part of successfully negotiating the financial terms of a deal. Usually the Licensor has a more optimistic view of the opportunity than the Licensee. In particular inventors and biotech companies who believe their product/technology is world-beating and who have a poor understanding of the commercial world, tend to have over-optimistic expectations of the value of their asset.

Sometimes the over-optimistic valuation has been used to raise funds from investors and therefore in negotiations the biotech management finds it difficult to accept a deal where the offer from the licensee/buyer is significantly less than their valuation. In this situation, the two parties can seek to bring their expectations closer together by sharing information regarding the valuation. Usually the valuation methodologies are the same e.g. both parties use NPV but the basic assumptions are different e.g. the assumptions underlying peak sales. One drug delivery company respondent said "Without agreement on sales potential there is little point negotiating".

However if the two companies are not prepared to share information, the negotiation becomes a horse trade. According to the PLG survey results over 75% of licensor/seller and licensee/buyer companies are prepared to share information about the size of the opportunity in terms of market size, market research results and peak sales (Chart 4). In addition over 50% of licensor and licensee companies are prepared to share financial data such as benchmarks, discount rate and NPV split. On the other hand there was a greater reluctance by licensors, than licensees, to disclose development costs and time, benchmarks, discount rates and NPV split and by licensees to disclose sales and marketing resources and costs.

While most companies are prepared to share information, there was a significant difference in willingness to share between types of companies (Chart 5). In general big pharma companies were more reluctant to share information. This may be because of big pharma strong negotiating position – they do not need to disclose and know the licensor is desperate for a deal with them, or they fear that the disclosed information will be used against them in the legal agreement e.g. for performance obligations. One biotech company said "Disclosure depends on the co-operativeness of the other party. Mutual disclosure is appropriate. Disclosure by one party and not the other is not appropriate"

Another company went to the heart of the matter saying, "I disclose anything that helps set realistic deal values but would redact or provide guidance rather than actual data if this is commercially sensitive".

Financial deal term expectations – share of project NPV

Once both sides have a broad understanding about the value of the product/technology, the next step is to agree how to split that value between licensor/seller and licensee/buyer. The survey asked respondents what is a 'reasonable' maximum and minimum share of project NPV that the licensee should receive (assuming a 20% cost of goods) for different stage licensing deals. The results, which were consistent with data presented at conferences in 2005 and 2009, showed that the earlier the project, the higher the share licensees should get of the total project NPV which makes sense given the higher risk for early stage projects (Chart 6).

On the other hand the PLG survey results for pharma and biotech/drug delivery in aggregate suggested that the licensee should get a much lower share than previous presentations e.g. somewhere between 40%-67% compared to 50%-85% depending on stage of project.

Chart 5

Willingness to disclose information by type of company

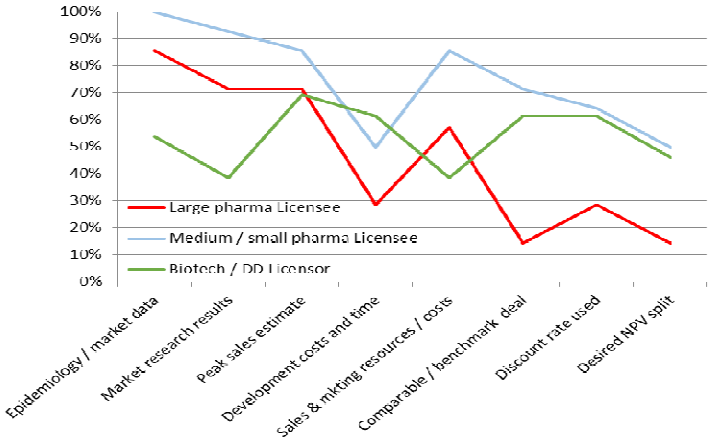
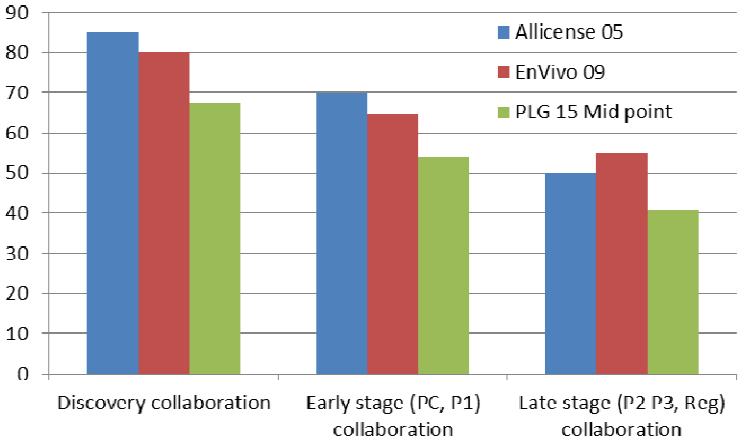


Chart 6

Licensee share of project NPV – PLG aggregate data



Although the share of NPV from the PLG survey aggregate data is generally lower than previous presentations, when the PLG results are limited to pharma respondents i.e. excluding biotech/drug delivery, the project NPV shares are roughly the same as the previous presentations in 2005 and 2009 (Table 1).

Table 1 – Licensee share of project NPV – PLG pharma data

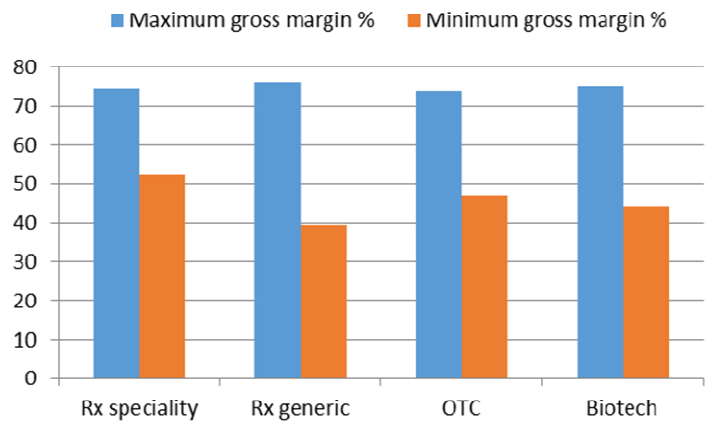
% project NPV to licensee	Allicense 05	EnVivo 09	PLG mid pt all	PLG mid pt pharma only	PLG mid pt biotech only
Discovery collaboration	85	80	67	78	60
Early Stage (PC, P1) collaboration	70	65	54	66	45
Late stage (P2 P3, Reg) collaboration	50	55	41	45	36

For an early stage collaboration, pharma expected a licensee to get between 59% and 73% (mid-point 66%) of the project NPV whereas biotech between 39% and 51% (mid-point 45%). In the authors' experience the biotech companies have unrealistic expectations or poor knowledge of pharma NPV calculations. Pharma licensees would never accept less than 50% of the project NPV (as pharma calculate it) for an early stage collaboration unless there were some special factors such as the biotech company incurring a high proportion of the development costs and risk.

Gross profit margins

For inward licensing projects, pharma companies usually have internal targets for minimum gross profit margins, defined as sales less cost of goods and royalty as a ratio of sales. The minimum gross margin is set to ensure the product will be profitable, at least in the medium term, after deduction of actual or forecast operating costs particularly sales and marketing. Biotech/ drug delivery companies need to be aware of the minimum gross margin as it may have a significant effect on the royalty rate that is acceptable to the pharma company. For example a pharma company with a minimum gross margin target of 65%, will be reluctant to accept a royalty of greater than 10% if the cost of goods percentage is 25%. The PLG survey asked the question what is the maximum gross profit margin that companies seek and what is the minimum acceptable? The results show that most companies seek a gross margin around 75% and a minimum in excess of 40% to 50%. As expected the generic companies are prepared to accept a lower gross margin than speciality pharma. The results are consistent with an analysis undertaken in 2012 by Medius of gross margins of public companies where the gross margin of Rx speciality companies was 75% on average and generic companies was 50%.

Chart 7 – Average maximum and minimum gross margins

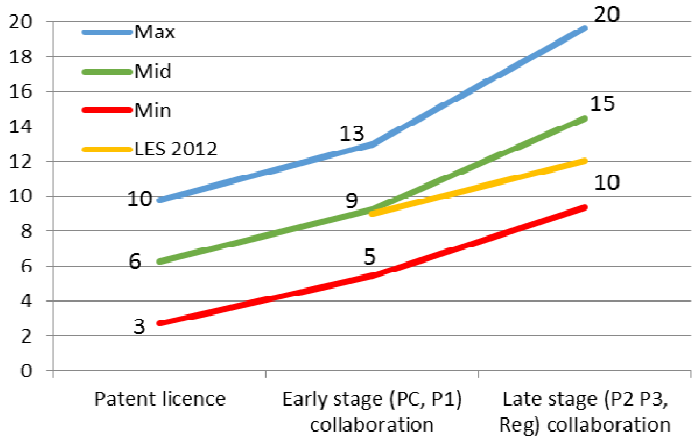


Financial deal term expectations – maximum and minimum royalty rates

There are less royalty data in the public domain than say upfront payments or aggregate milestones. To get a feel for royalty rate expectations, the PLG survey asked what are acceptable maximum and minimum royalty rates for three different types of licensing deals, a patent licence, an early stage and a late stage deal, assuming a 20% cost of goods and no royalty stacking. Unlike with share of NPV, there was no significant difference between pharma and biotech responses. Also the results showed, as expected, that the levels of royalty were higher for later stage projects (Chart 8).

The median of the maximum values gave royalty rates of 10%, 13% and 20%, respectively, and minimums of 3%, 5% and 10%. The mid-point between these values was compared to the results of the LES survey undertaken in 2012 ("Global BioPharmaceutical Royalty Rates Deal Terms Survey"). The surveys were different in design so the results are not strictly comparable. For example the LES analysed royalty rates as either flat or tiered for preclinical, pre proof of concept (POC) or post POC licensing deals. Nevertheless the PLG survey results are similar to the LES for pre POC where both surveys had a value of 9% and rising post POC to 12% for LES and 15% for PLG (Chart 8).

Chart 8 – Maximum, minimum and mid-point royalty rates compared to LES survey



Range of royalty expectations

In Chart 8, the median of the maximum and minimum royalty rates is shown together with the mid-point for projects at various stages. However the median is not the whole story because of the distribution of individual values around the median. For all types of deals there was a group of values for maximum royalty rates at the high end which skewed the median. For example using the early stage collaboration as an example, the median maximum royalty was 13% but 33% of the observations were at 20% (Chart 9a). The minimum royalty rates were less distorted (Chart 9b). The existence of a large number of observations at the high end for maximum royalty rates was primarily from the biotech / drug delivery respondents. These companies are usually licensors and have higher expectations of royalty rates. "When the final result is expected to be a compromise, it is often prudent to start from an extreme position" (John Maynard Keynes).

Chart 9a Distribution of maximum royalty rates

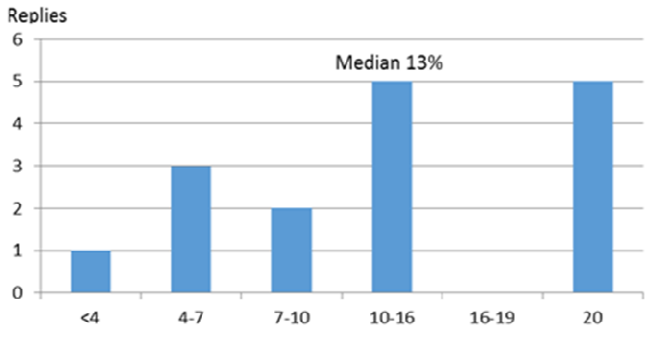
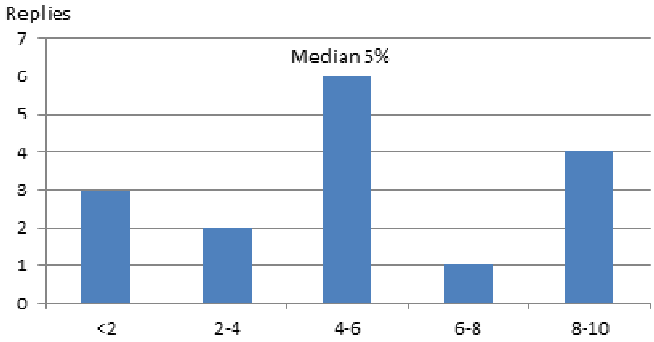


Chart 9b Distribution of minimum royalty rates



Product acquisition multiples

The business model for some pharma companies such as Valeant, Meda and Alliance Pharma plc is based on product (and company) acquisitions rather than internal or external R&D to develop and launch new products. The price for such acquisitions is often measured as a multiple. The survey asked the question "When making product acquisitions what are maximum and minimum acceptable multiples of sales, gross profit, EBITDA, EBIT and post-tax profit?" Most respondents referred to the price/sales ratio or the price/EBITDA ratio. In terms of a sales multiple, the median maximum was 3 (average 4) and the median minimum was 2 (average 2). The EBITDA ratios ranged from 7 to 14.

Table 2 Price/sales multiples for product acquisitions

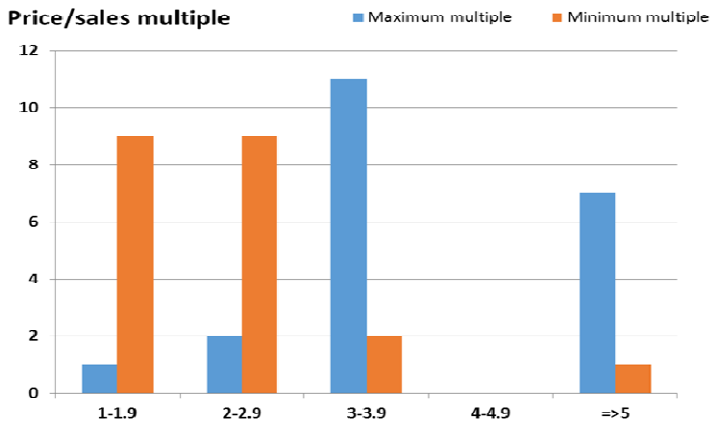
	Median	Average
Maximum	3	4.1
Minimum	2	1.9

The difference between the median and average for the maximum sales multiple is explained by one third of the data points having multiples of 5 or more, mostly 5 to 6 (Chart 10). Although the vast majority of published product acquisition sales multiples are in the 2 to 4 range, there are higher ratios dependent on the specific product's gross margin and sales growth. A product with static sales and a low margin will be less than one with sales growth and a high margin unless of course the acquisition is "strategic" in which case virtually any multiple will do! Two examples may demonstrate the effect of different growth potential and/or gross margin. In July 2015 AstraZeneca divested Entocort to Tillotts/Zeria for a price/sales multiple of 4 and Caprelsa to Sanofi/Genzyme for 6.25. Entocort has been on the market for 20 years whereas Caprelsa (vandetanib) is a rare disease medicine launched in 2011.

Financial training of business development and licensing executives

Both of the authors are finance module tutors on the distance learning Healthcare Business Development and Licensing MSc, a course set up jointly by the PLG and the University of Manchester and teach Finance at the German and UK PLG courses. The survey included the question: "In your company, what type of financial training is available to BD executives?" The results show that, as expected, large companies have the most training opportunities mostly from in-house and 'on the job' training rather than external courses (Chart 11). Mid-sized companies focus on 'on the job' training supplemented by external courses and small companies use mainly PLG courses but 30% do no training at all. One company said "We would pay for experience, we don't have time to train people".

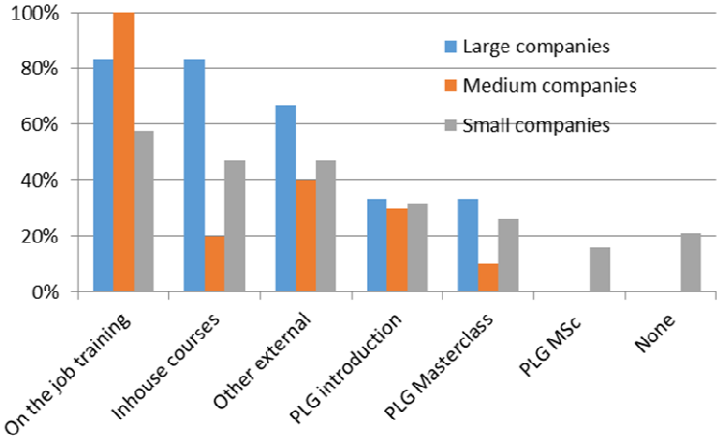
Chart 10 Price/sales multiples for product acquisitions showing skewed maximums



Conclusions

Why has valuation of deals gone up following the financial crisis? We can exclude that the cheap money is driving up calculations or increasing the number of R&D projects. We undertook a survey to verify the methodology used for value calculation. NPV and risk-adjusted NPV remain the main methods but compared to a previous analysis, we found that benchmarking has gained importance: Follow the crowd and the trend is in times of scarcity of new ideas and targets an indication of exaggerated deal terms. It might be wise to follow a solid analysis and not to overpay – in case the company's own pipeline does not require desperate actions.

Chart 11 Financial training opportunities by size of company



There is a willingness by most companies to share information but big pharma is more reluctant. Once the value of a product is estimated, the pharma companies in the survey had the same share of value (NPV) between the Licensor and Licensee for different stage deals as reported at previous conferences. In contrast the biotech and drug delivery companies believe that the pharma shares would be much lower, even lower than 50%. This is a triumph of hope over reality. The same applies to some of the outlier product acquisition sales multiples (as high as 10) and royalties (as high as 35% or more). But, overall the survey confirmed that most companies have a similar view about what is 'reasonable' and it is consistent with results seen in previous surveys by the PLG and other organisations.

The survey showed that the methodologies used are at a very high and suitable standard within the industry and the training and educational level is generally high. In smaller companies, however, emphasis needs to be applied to the education of qualified BD people in order to get fair shares of future profits. Multiple options exist for smaller companies to build in-house expertise, such as the residential PLG and online courses (University of Manchester).

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Discovery & Development: Partnering with Patient-led Research Networks

Business development and licensing executives at a diverse range of life sciences companies gain concrete advantages through partnerships with patient-led research networks. There are increasing numbers of these typically single disease-focused patient groups participating in the discovery and development of drugs, diagnostics and devices. More than a few have successfully brought assets from early to later stages of development. Found around the world, these networks most often do not compete with industry. Instead, they seek to partner with industry, recognising that they cannot commercialise their assets. As such, they represent a substantive opportunity to enhance companies' business objectives for in- and out-licensing.

By Yvonne Schlaeppi, JD, non-executive director and advisory board member; Mark Krueger, MPH, president, MK&A; Veronica Lopez, MPH, strategic associate, MK&A

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As demand for new treatments and related health care solutions rises, there is a growing trend for patient groups to become actively involved in shaping the drug, diagnostic and device research agenda. These groups, known as patient-led research networks (PLRNs), understand the needs of the patients and the carers they serve. Their efforts, largely independent of industry partners, have already resulted in compounds, diagnostics and devices and relevant insights attractive to industry. Given the growth in number and maturity of PLRNs, the opportunities for business development and licensing (BD&L) executives to advance shared interests are available in increasingly large numbers.

PLRNs have a unique perspective on their particular therapeutic area or disease and the relevant market. In addition, many have the personnel and infrastructure to identify, evaluate and/or perform early development of promising drug, diagnostic and device candidates. By accessing the knowledge and networks of PLRNs, BD&L executives may gain a significant competitive advantage.

This article provides an overview of PLRNs; describes their relevance to licensing; examines the work of representative organisations; and suggests practical ways for companies to partner with PLRNs.

Overview of PLRNs

Patient groups serve a variety of functions from patient-focused support and education to political activity and professional education. Some patient groups focus on research promotion, offering traditional research grants and lobbying for research budgets.

A subset of these groups, PLRNs, take a more active role in shaping the research agenda by funding and executing the identification and validation of experimental assets, which they either own or to which they have licensed rights.

PLRNs are organised by advocates to bring greater urgency and focus to drug treatment and diagnostic and device development. These networks provide financial support for basic and clinical research. Some funding is directed to their own laboratories. Other financial and in-kind support goes to external investigators and to pharma, biotech, diagnostic and device companies which have a research agenda reflecting patients' verified needs and preferences. Decisions are often made using peer review models.

PLRNs' relevance to BD&L

Partnering with PLRNs provides useful competitive intelligence to industry executives. PLRNs provide access to specialised data and insights into patients' and providers' preferences and unmet medical needs. They can also provide a window into pipelines of promising therapeutic approaches and experimental agents. Establishing trusted relationships with well-positioned PLRNs can lead BD&L to receive early notification of new developments and the opportunity to in-license compounds or devices. In addition, some PLRNs may be appropriate partners for out-licensing a company's assets.

Industry partners also gain the opportunity to learn from the best minds in the field through PLRNs' research consortia and advisory groups. Although directed by and responsive to patients, carers, and their advocates, PLRNs are often counseled by medical and scientific advisory boards. These advisory boards may provide industry partners with opportunities to learn from leading basic scientists and clinical researchers and other reputable experts, not just from those with whom they have an existing relationship. PLRN investigators typically represent the most current thinking in the field and the networks themselves are inclusive and driven by a commitment to excellence. Industry can profit from engagement with these experts through unbranded conversations.

Representative PLRNs

Benefits to BD&L from working with PLRNs are best exemplified by the well-known partnership between the Cystic Fibrosis Foundation (CFF) and Vertex. Through funding from CFF, Vertex developed the breakthrough therapy, Kalydeco (ivacaftor), which treats the underlying cause of cystic fibrosis (CF) in a subset of patients with a certain gene mutation (Fda.gov, 2012). Previous therapies only treated the symptoms of CF (Fda.gov, 2012). Former US FDA commissioner Margaret A. Hamburg, MD noted that "Kalydeco is an excellent example of the promise of personalised medicine – targeted drugs that treat patients with a specific genetic makeup.

The unique and mutually beneficial partnership that led to the approval of Kalydeco serves as a great model for what companies and patient groups can achieve if they collaborate on drug development" (Fda.gov, 2012). Kalydeco treatment in the US costs over US$300,000 per year (Risser, D. and Gilblom, K., 2014). In 2014, CFF sold its royalties to Royalty Pharma for US$3.3bn, funds which CCF is using to accelerate the development of other therapies and for the care and support of people living with CF (Cff.org, 2015). The drug was also approved by the European Medicines Agency (EMA) and Health Canada.

The Leukemia and Lymphoma Society (LLS), a well-known patient group, also includes a PLRN among its offerings. LLS currently funds six companies from around the world – Celator Pharmaceuticals, Kiadis Pharma, Kite Pharma, OXiGENE, Stemline Therapeutics and Valor Biotherapeutics – through its Therapy Acceleration Program (Lls.org, 2016). These projects help industry gain clinical proof of concept data and resources needed for the testing, registration and marketing of diagnostics, therapies, and supportive care for leukemia, lymphoma and myeloma (Lls.org, 2016). For example, LLS made an approximately US$1m equity investment in Kiadis targeted at funding the Phase 2 investigation of the repeated dosing of its compound ATIR101™ (Lls.org, 2016).

The French Muscular Dystrophy Association (Association Française contre Les Myopathies or AFM), has advanced the treatment of muscular dystrophies and other rare diseases through multiple partnerships and collaborations with industry.

Trophos, recently acquired by Roche, developed olesoximo (TRO19622) for the treatment of spinal muscular atrophy (Roche.com, 2015). Trophos' shareholders received €120m upfront, plus payments based on predetermined milestones worth up to €350m (Roche.com, 2015). AFM, which supported the development of the treatment, retained exclusive rights to olesoximo during the acquisition and the option for the rights to revert back to the organisation in case of treatment deprioritisation. Olesoximo was granted orphan product designation by both EMA and FDA (Roche.com, 2015).

AFM is also co-founder and the main financier of the French Foundation for Rare Diseases (Fondation Maladies Rares), a joint project to encourage and streamline research into rare diseases in France (Afm-telethon.com, 2016).

In 2011, AFM founded the Biotherapies Institute for Rare Diseases, four labs which advance orphan products discovery and development in Europe and around the world (Afm-telethon.com, 2016). Genethon, one of the laboratories founded by AFM, recently announced a partnership with Audentes Therapeutics to co-develop a treatment for X-Linked Myotubular Myopathy (XLMTM) (Genethon.fr, 2014).

"a joint project to encourage and streamline research"

> a qualified intermediary can facilitate the process

Genethon initiated the development of the novel drug candidate using gene therapy technology in 2009 (Genethon.fr, 2014). Genethon's product, which presented the first demonstration of persistent disease correction of a neuromuscular disease through the single delivery of a gene therapy treatment in large animal models, will be developed and brought to market by Audentes (Genethon.fr, 2014).

PLRNs seek to advance the development of promising therapies, diagnostics and devices through partnering with industry. They out-license or co-develop their experimental agents with industry, while also providing financial, technical and in-kind support. Each partnership, no matter how it is structured, must acknowledge intellectual property rights contributed or licensed at the start of development, as well as rights to intellectual property generated during research and development. Those "IP rules of engagement," as well as compliance with the privacy regulations governing patient data, have to be established early in the cooperation between industry and the PLRN.

Practical tips for engaging PLRNs

The first step for a company entering the arena is to understand PLRNs operating in the desired therapeutic indication and how their priorities align with those of the company. The evaluation process includes collecting data on multiple groups and assessing each potential PLRN partner against the company's BD&L needs using pre-determined criteria. Making an effective assessment relies on an in-depth understanding of each group's potential fit. Gaining that level of familiarity with privately led and funded PLRNs often requires years of careful relationship and trust building. Industry can save significant amounts of time and effort by engaging a knowledgeable intermediary to provide detailed knowledge of and help prioritising PLRNs.

After the highest priority PLRNs are identified, the company is ready to make contact with them, profiting from existing company relationships where extant. Here too a qualified intermediary can facilitate the process by quickly delivering meetings with key leaders of the target PLRNs. Industry will benefit from prior internal conversations about patient reported outcomes, patient centricity, and procedures for building strong and compliant relations with patient groups, as these topics may arise during meetings. BD&L executives need not be experts – only knowledgeable enough to engage in meaningful conversation. External counsel can advise on the groups' likely interests and appropriate responses.

Intermediaries can also help organise meetings and other opportunities for PLRNs to present their best assets to the company. This will involve clearly defined goals and expected outputs as well as agreement on confidentiality of any information shared. These meetings can also send a powerful signal of the sponsor's interest in partnering with PLRNs for in- and out-licensing.

When building a broader presence and a network of PLRNs, industry players must understand how to manage their partners' expectations, including financial support. Companies should feel no obligation to provide gifts or grants. Indeed, donations may create an unwanted impression that the company is committed to a particular PLRN in the field, when in fact it is constantly surveying multiple opportunities. Contracts can be put in place, should an asset of interest be identified.

Conclusion

Although there are several high profile examples of successful collaborations between industry and PLRNs, this type of cooperation is still a relatively new concept.

The main difference between partnering with patient groups in the traditional way and partnering with PLRNs is that the latter can deliver a tangible research asset for commercial development. BD&L executives working with suitable PLRNs can meet their goals while gaining a broader and deeper understanding of patient outcomes and patient benefit/risk preferences than would otherwise be possible. The advantage gained by partnering with PLRNs is essential to staying ahead of the competition.

Key points

- Partnering with PLRNs can advance BD&L goals when properly structured
- PLRNs provide multiple competitive advantages, from granting insights into patients' preferences to tapping expert knowledge and delivering experimental agents for further development
- Engagement of PLRNs through qualified third parties may help companies identify relevant groups more quickly and engage in respectful, mutually beneficial relationships with long-term promise

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PLG News

Conference Report: PLG UK & OTCToolbox

FMCG + Pharma = Consumer Healthcare?

In March 2016 the first conference on Business Development and Innovation Opportunities in Consumer Healthcare/OTC organised by OTCToolbox and the Pharmaceutical Licensing Group was held in London. This international event was the first to focus exclusively on business development and innovation in the consumer healthcare/OTC market, and comes at a time of unprecedented change for the industry.

Most of the delegates came from Europe with a few from North America and India. The speakers were from primarily FMCG companies such as Reckitt Benckiser (RB) and Unilever, and from primarily pharmaceutical companies such as Boehringer Ingelheim and Thornton and Ross (Stada). This provided an interesting contrast in the approach to the consumer healthcare market.

The primarily FMCG companies such as Reckitt Benckiser and Unilever are heavily focussed on consumers and talk about "thinking beyond discovery of drugs" and "digital technology is the future" especially amongst the millennial generation born since 2000, whereas the primarily pharma consumer healthcare companies take a more traditional approach to marketing driven by their pharma heritage.

Roberto Funari, Executive Vice-President, Category Development Organisation at Reckitt Benckiser questioned how retailers and pharmacies would adapt to the digital age. For example, would there be 'virtual shelves'?

The impact of digital technology on healthcare is becoming increasingly important and as a result the PLG held the conference at the St Pancras Renaissance Hotel, London on 19th May.

To put into context what consumer healthcare companies are doing in business development, Deborah Wilkes of OTC**Toolbox** presented the trends from 2015 including mega OTC deals reshaping the global OTC industry, big pharma including OTC businesses in asset swaps, generic companies building an OTC presence and smaller companies acquiring brands. She said OTC consolidation showed no signs of slowing. Some companies such as J&J have a mixed business model with pharma, devices and consumer healthcare while others are spinning out OTC as a separate company or business.

In terms of separating the OTC business within the company, Oliver Freichel, Corporate Vice President BD, Strategy and Rx to OTC Switches at Boehringer Ingelheim Consumer Health Care explained, the benefit of a separate OTC business in terms of cost transparency, the ability to restructure the portfolio and make the business more attractive based on cross functional teams with clear key performance indicators. The need for cross functional teams, including for example regulatory affairs, was reinforced by the presentation from Dorothee Klöpf, Senior Manager Regulatory Affairs at Diapharm and Annemarie Dengler, Director Business Development at red OTC development. They explained that product innovation is a must with 25% of OTC products in Germany originating in the past five years. There are a number of product innovation and regulatory options for companies to consider when developing, a medicinal OTC product, a food supplement, a cosmetic and a medical device.

Roberto Funari, Executive VP at Reckitt Benckiser, presents **The Future of OTC Medicines**

The examples they showed demonstrated some of the challenges with each of these options to deal with constantly changing regulatory requirements.

Although the FMCG and pharma companies have a different approach to the market, their approach to innovation and business development is similar. Both rely on continual internal innovation and external collaborations to develop new products. According to Jonathan Hague, Vice President Open Innovation at Unilever, 54% of the value of the pipeline is from partnerships with universities and companies.

The importance of innovation was also mentioned by Andy Tisman, Global Senior Principal for Consumer Health at IMS Health. In Western Europe and North America innovation including line extensions and Rx to OTC switches accounts for two thirds of growth. The main area of growth is emerging and developing markets which accounted to 73% of global growth in the 12 months to the end of September 2015.

So the challenge is how to achieve growth in mature markets such as Western Europe and North America. In this area, the top ten consumer healthcare companies are growing less than the market demonstrating that smaller companies are more adept at innovation.

This adeptness at innovation was amply demonstrated by Dieno George, CEO of Thornton and Ross who showed how a sales increase of 300% was achieved in the 12 year period between 2001 and 2013. It was based on acquisition of 21 brands without external funding, the launch of a novel head lice preparation that now accounts for about 40% of the UK market and constant innovation in terms of line extensions of existing brands. A similar story for an SME company was presented by Yvan Vindevogel, who is founder and CEO of Damier Group and Executive Chairman of Vemedia Consumer Health. Like Thornton and Ross, Vemedia grew by a combination of acquisitions and innovation but in this case supported by external funding.

But acquiring and developing brands is not sufficient, value creation in consumer healthcare requires a mixed business model with both FMCG and pharmaceutical capabilities. By implication a company driven by a large FMCG or pharmaceutical parent may not be able to successfully combine these capabilities effectively in a relatively small consumer healthcare division and may explain why SMEs are more adept at innovation.

The level of interest in this conference was very high, with around 150 delegates present. Delegates commented that it provided a facility for consumer healthcare companies to exchange views and to network like they are able to do at similar conferences for pharmaceutical and biotech companies. There will be a second OTC Conference and Networking Event in London on 2nd and 3rd of March 2017. Don't miss it!

In-depth reports of the conference are available from OTCToolbox www.otctoolbox.com

Pharmaceutical Licensing Groups European Events

PLCF Training - Market Research Applied to BD&L — **www.plcf.org**
Thursday 16th June - Cercle de l'union Interalliée, Paris

PLCF Training - Market Access — **www.plcf.org**
Wednesday 14th September - Cercle de l'union Interalliée, Paris

8th European Pharmaceutical Licensing Symposium — **www.plg-group.com**
Thursday 22nd & Friday 23rd September - Radisson Blu Royal Hotel, Brussels

PLG UK Evening Presentations & Networking Reception — **www.plg-uk.com**
Wednesday 19th October - Bird & Bird Offices, London

PLG Spain XVI General Assembly — **www.plgs-spain.com**
Thursday 20th & Friday 21st October - Valencia

NPLG Autumn Networking Dinner — **www.nplg.org**
Wednesday 2nd November - Kurhotel Skodsborg, Skodsborg

PLCF Training - Negotiation Skills — **www.plcf.org**
Wednesday 9th November - Cercle de l'union Interalliée, Paris

PLCD Seminar - The Perfect Term Sheet: Interactive Case Study — **www.plcd.de**
Monday 14th - Wednesday 16th November - Hilton Gendarmenmarkt, Berlin

PLG UK Training - Introduction to Healthcare Business Development — **www.plg-uk.com**
Wednesday 16th - Friday 18th November - Marriott Lingfield Park

PLCD Autumn Meeting — **www.plcd.de**
Thursday 24th & Friday 25th November - MARITIM Hotel, Bremen

PLG UK Evening Presentations & Drinks Reception — **www.plg-uk.com**
Thursday 15th December - Gowling WLG Offices, London

PLG UK Training - Early Stage Healthcare Business Development — **www.plg-uk.com**
Thursday 15th December - Gowling WLG Offices, London

2nd OTCToolbox & PLG OTC Conference and Networking Event — **www.plg-uk.com**
Thursday 2nd & Friday 3rd March 2017 - Hilton London Tower Bridge, London

NPLG AGM & Networking Dinner — **www.nplg.org**
Thursday 9th March 2017 - Kurhotel Skodsborg, Skodsborg

Medius Deal Watch

"This is the way the world ends, not with a bang but a whimper"[1]

And so it was with Pfizer's acquisition of Allergan. The big splash from the 3rd biggest corporate M&A deal worth $160bn announced in November 2015 collapsed in April 2016 as a result of some arcane change in tax regulations. Pfizer's dogged determination to achieve a tax inversion can only be described as a fiasco and given, that this was the second time of trying, perhaps fiascos, is more appropriate.

By Roger Davies, Medius Associates Ltd.

About the Author

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Winners and losers of the Pfizer / Allergan Debacle

One can certainly sympathise with Pfizer and other large multinational companies with a tax base in the US where the corporate tax regime is not fit for purpose and where the dysfunctional political system means the politicians have completely failed to find a consensus and enact new legislation. The prospect of a divisive figure becoming President does not bode well for a consensus in future. Hopefully Pfizer has finally got the message from the US Government and will now focus on developing its long term business as a leading pharmaceutical company rather than seeking a short term financial 'fix' to improve its financial results.

Winners	Losers
US Government (possibly short term gain)	Pfizer - loss of tax gain
Allergan $150m break-up fee to cover costs	Pfizer – costs of bid plus break-up fee
	Banks advising the companies loss of fees $200m*
	Hedge funds betting on deal lost $700m*
	Allergan shareholders as share price dropped nearly 20% from $270 to $220
Non US countries where Pfizer has parked $80bn**	Non-US target companies hoping for a bid from a US company to achieve tax inversion
Allergan 30,000 employees who faced lay offs	Brent Saunders as possible CEO of Pfizer

**Source: Times 7th April 2016 **Economist 9th April 2016*

"Pick yourself up, take a deep breath, dust yourself off and start all over again"[2]

Allergan must have known for some time that the Pfizer acquisition was likely to collapse because on the same day as the announcement, Allergan announced a $3.3bn deal with Heptares for early stage M_1/M_4 agonists for treating Alzheimer's. The deal value is heavily back end loaded with 75% of the value dependent on milestones linked to sales performance and the upfront and R&D payments representing only 5% of the headline value.

Two weeks later Allergan announced what is probably another back end loaded deal with the acquisition of Topokine for $85m upfront and undisclosed milestones. Topokine develops topical products for fat reduction and has a product in phase 2b/3 for treatment of 'undereye bags'. [Did you know: 40m Americans *suffer* from this condition!] This product fits perfectly with Allergan's presence in the dermatology / aesthetics market but the Alzheimer's deal is a surprise given the limited R&D Allergan has in that area and the high risk of failure.

AbbVie is another company who "picked themselves up". Like Pfizer, AbbVie was also wounded by a change in tax inversion rules forcing it to withdraw from its $54bn acquisition of Shire in October 2014. However within six months AbbVie announced the $21bn Pharmacyclics acquisition, won against competition from J&J.

This month the AbbVie oncology deal wagon rolls on with the highest value deal of the month, the acquisition of the 'unicorn' company Stemcentrx for $5.8bn ($2bn cash, $3.8bn stock) plus $4bn in cash payments for success-based regulatory and clinical milestones.

It is assumed that the majority of the $4bn milestones are linked to the four early stage clinical compounds in development also being acquired. Stemcentrx represents a good fit with AbbVie's oncology portfolio and is forecast to generate multibillion $ revenue. Its lead compound, Rovalpituzumab tesirine (Rova-T), is a biomarker-specific antibody drug conjugate, in phase 1/2 targeting cancer stem cell protein DLL3. Rova-T showed a 44% overall response rate in DLL-expressing small cell lung cancer (SCLC) patients who had failed one or more standard therapies.

Not content with the Stemcentrx acquisition, in April AbbVie also closed two other oncology deals:

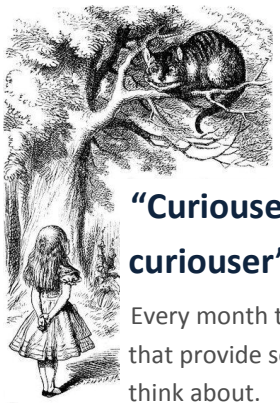
- ◊ With CytomX, a co-development and co-commercialisation of a Probody drug conjugate against CD71
- ◊ With Argenx in Belgium, a co-development and option to license of ARGX-115 a preclinical human antibody programme targeting the novel immuno-oncology target GARP, a protein believed to contribute to immuno-suppressive effects of T-cells.

A 'Unicorn' is a mythical beast which is hard to catch, or it is a start-up company where the valuation has exceeded $1bn'

One of the interesting aspects is the comparison of the deal terms in these two preclinical deals.

	CytomX	Argenx
Deal Type	Co-development and co-ommercialisation	Option to license
Preclinical and early clinical development	CytomX leads	Argenx undertakes R&D until IND, AbbVie thereafter if option exercised
Late clinical development	AbbVie leads with costs shared	AbbVie
Commercialisation	AbbVie leads, CytomX option to co-promote in US	AbbVie, Argenx option to co-promote in EU and Switzerland
Upfront	$30m	$40m
Milestones	$470m	Preclinical $20m and $625m
Other payments	US profit share, outside US tiered double digit royalties	Two year R&D funding , tiered **up to** double digit royalties

Both deals have similar upfront payments, the licensor leading the early development and the licensors having options to co-promote. However the Argenx deal is an option not a licence and has lower royalty rates. An option is usually less attractive than a licence to a biotech company because an option does not give such a strong endorsement of the technology. Argenx may have been in a weaker negotiating position compared to CytomX. This is the first big pharma deal for Argenx whereas CytomX has a track record of deals with Pfizer and BMS. Agrenx also has a shorter cash runway than CytomX. These factors give big pharma licensees the upper hand in negotiations unless they are in competition with other big pharma companies for the same asset.



"Curiouser and curiouser"[3]

Every month there are deals that provide something to think about.

For example one option deal this month is between Enumeral and Pieris. Under this agreement Pieris pays $0.25m to obtain a licence to Enumeral's 388D4 anti-PD1 antibody programme. Within two months, Pieris either pays another $0.75m or the licence terminates. If Pieris pays, the development milestones are $37.8m and the sales milestones $67.5m.

Pieris also gets a further 12 month option to another antibody programme and pays an additional fee if it is exercised. This arrangement suggests that Pieris may not have had full access to the confidential information regarding the technology and had to pay a fee of $0.25m for the privilege.

Whilst the multiple options are interesting, the amusing aspect of this deal is the description of the royalty rates as "low-to-lower middle single digits". Presumably this means 1% to 4%. It is amazing how companies tie themselves in verbal knots trying to describe the royalty rates without mentioning the number. Does anyone think that the disclosure of 1% to 4% is going to make any material difference to the opinion of investors or other interested parties?

Another deal worth pondering about is the $265m exclusive licence by AstraZeneca (AZ) of the approved Zurampic (lesuranid) plus a fixed dose combination with allopurinol for treatment of gout. Ironwood is paying $100m upfront for the US market plus $165m of milestones and "tiered single digit royalties". The question is why is AZ not marketing the product? The reason according to AZ is Ironwood will ensure a successful launch of *Zurampic* in the US, "while allowing us to concentrate our resources on the innovative medicines in our main therapy areas". Annual US sales of Zurampic are estimated by Ironwood at $300m so it seems strange AZ did not market the product using a contract salesforce if needed.

"Next time you're found, with your chin on the ground, there's a lot to be learned, so look around"[4]

In the last four years Gilead sales have grown from $8bn to $32bn (CAGR 40%), mainly driven by Sovaldi and Harvoni for hepatitis, resulting in a cash pile of over $20bn.

In spite of this cash mountain, Gilead has not made any major acquisitions to maintain growth. The latest deal in early April was the acquisition of Nimbus Apollo for $0.4bn upfront plus $0.8bn in milestones. Nimbus develops Acetyl-CoA Carboxylase (ACC) inhibitors for treatment of liver diseases with the lead compound, NDI-010976 in phase 1 for non-alcoholic steatohepatitis (NASH - a hot area this month with deals by Regeneron, Madrigal and Tobira).

The deal with Nimbus did not excite investors and they were even less impressed when Gilead reported first quarter results showing sales growth of 4% and full year guidance of $30bn sales i.e. less than 2015. As a result the share price dropped by nearly 10%. According to Reuters, the CEO of Gilead said "M&A is always a process," noting that Gilead has never said it would be unwilling to pursue a hostile deal, although "we do prefer a friendly process." This doesn't sound like a company aggressively seeking major deals.

As usual, most of the deals this month are in oncology. Apart from the three deals by Abbvie, there were deals by GSK and Janssen with Zymeworks and Tesaro respectively. GSK must have liked working with the Canadian company Zymeworks because it is the second collaboration in less than six months. The collaboration provides GSK with a platform technology to develop bispecific antibodies. Zymeworks, like CytomX, have multiple Big Pharma partners including Merck & Co and Lilly. The upfront and preclinical milestones of $36m is similar to the AbbVie payments to CytomX and Argenx all for preclinical development. At first glance it is surprising therefore that Janssen is only paying $85m ($35m upfront plus $50m equity representing < 20% of total headline value) for niraparib, a phase 3 molecule which Tesaro licensed from Merck & Co in 2012.

Top deals in April 2016 by headline value

Licensor / Acquisition target	Licensee / Acquirer	Deal type	Product /technology	Headline $m
Stemcentrx (US)	AbbVie (US)	Company acquisition	Phase 1 antibody drug conjugate targeting cancer stem cell protein DLL3	9,800
Heptares (JP)	Allergan (IE)	License and collaboration	Phase 1M1/M4 agonists for Alzheimer's disease	3,340
Nimbus Apollo (US)	Gilead (US)	Company acquisition	Phase 1Acetyl-CoA Carboxylase (ACC) inhibitor program for liver disease	1,200
ZymeWorks (US)	GSK (UK)	Licence and option	Preclinical bi-specific antibodies based on Azymetric platform for treatment of solid tumours	908
Argenx (NL)	AbbVie (US)	Option to licence and co-promote	Preclinical ARGX115 antibody programme targetting GARP protein for treatment of cancer	685
CytomX (US)	AbbVie (US)	Licence and option to co-promote	Preclinical CD71 Probody Drug Conjugates for 3 targets for treatment of cancer	500
Tesaro (US)	Janssen (US)	Licence and collaboration	Niraparib PARP inhibitor in clinical phase for treatment of prostate cancer	450
AstraZeneca (UK)	Ironwood (US)	US licence and commercialisation	Lesinurad (approved) + combo in development for treatment of gout	265
Intellia (US)	Regeneron (US)	Co-devt & co-commercialisation	Discovery stage CRISPR/Cas platform for treatments of liver disease	125
Enumeral (US)	Pieris (DE)	Licence & option to further programme	Discovery stage 388D4 programme of PD1 monoclonal Antibodies immunotherapies	106
Topokine (US)	Allergan (IE)	Company acquisition	Topical medicines for fat reduction	85
Dong A (SK)	Tobira (US)	Cross licence*	Evogliptin in combination with cenicriviroc (CVC)	72
Synta (US)	Madrigal (US)	Company acquisition	Phase 1 compound for treatment of liver disease	61
Celgene (US)	Juno (US)	Option exercised to extend territory	Phase 2 CD19-based CAR T therapies for treatment of leukaemias	50
Acerus (CA)	Aytu (US)	US license and commercialisation	Approved nasal testosterone for treatment of hypogonadism	46

All deals global unless otherwise stated

**Dong A has commercialisation rights in South Korea, Tobira in Australia, Canada, Europe, United States*

The explanation for this is that Janssen is getting rights only for prostate cancer, not ovarian and breast cancer where the product is in phase 3 and the rights do not include Japan. Licensing one indication for a new product is unusual not least of all because of potential pricing issues if niraparib is launched by different companies at different prices. To deal with the development risk, Janssen has the right to terminate if there are any safety concerns or (without cause?) after two years from date of signature.

"And the end of all our exploring will be to arrive where we started"[5]

This article started with the controversy surrounding an acquisition and ends with the controversy of another acquisition. This time it is not a Big Pharma deal being blocked by US Government but a Big Pharma deal (by Sanofi) blocked by Biotech (Medivation). The press release and letter released by Sanofi reads like a rejected suitor's kiss and tell story. Sanofi would like to merge with Medivation as it makes "strong strategic sense".

Unfortunately the Medivation CEO, David Hung, was not interested in a meeting or even hearing Sanofi's proposal. So feeling rejected and unable to make its case, Sanofi sent a letter explaining why the merger would be beneficial to both sides and offering a dowry in the form of a cash deal worth $9.3bn (representing 38 x 2015 post tax profit with a share price premium of over 50%).

Medivation gave Sanofi the cold shoulder and did not reply. After two weeks, Sanofi decided to make the rejection public presumably in the hope that the Medivation shareholders would put pressure on the CEO to accept Sanofi's offer.

But this was not to be because on 29th April the Medivation Board rejected the offer as it "undervalues Medivation and is not in the best interests of the company and its stockholders".

Like all kiss and tell stories, the suspicion is that Medivation has a better offer from other suitors. The rumour is that Astrazeneca, Pfizer and Novartis are showing interest. Sanofi's experience may explain why **"April is the cruellest month"**[6].

No doubt this story will run and run…

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