termsheet

PharmaVentures
Experts in deals and alliances

January 2017 Issue 20

Heads of Terms
The Art of the Deal

Negotiation strategies and tactics have come to the fore again as the UK enters negotiations with the European Union over Brexit, and as Donald Trump talks about re-negotiating NAFTA and other trade deals. We will all watch as a number of self-professed experts enter into the 'art of the deal'.

Taking an extreme position when opening a negotiation in the hope of settling for an outcome in the middle ground is an oft-touted strategy of effective negotiation. But this technique is not without its drawbacks; often resulting in a loss of credibility due to a greater loss of ground from one's opening stance. It is also a precarious strategy if your original position is not defensible. You can look inexperienced, naive or just plain stupid! Furthermore, posturing techniques often result in a lack of trust on the other side, undermining the ability of both parties to reach a satisfactory agreement.

In those instances, where ongoing relationships aren't required, or where one party is particularly weak and desperate to do a deal, cultivating trust in the long run may not be important. But deals that require post-agreement cooperation, such as licensing agreements and alliances, do require on-going trust, and such heavy-handed tactics can lead to poor outcomes.

When advising our clients, we work hard on fact-based negotiating positions and ones which are both credible and defensible. The migration from a realistic opening position to an agreed position between both parties results in a better deal, whereby both parties have cooperated to get a true win-win outcome.

When it comes to Trade agreements, future ongoing trust is required. It will be interesting to watch how such negotiations play out over the next few years.

Dr Fintan Walton
Chief Executive,
PharmaVentures Ltd.

industry insight

Optimising the path to commercialisation
Who can help and when?

Adrian Dawkes
Managing Director, PharmaVentures Limited

At PharmaVentures we have been providing commercialisation advice for 25 years for pharmaceutical, biotech, diagnostics and device companies. The nature of that advice stretches from commercialisation strategy to valuation, licensing and M&A execution. We are frequently asked by companies with drugs in the early stages of development (preclinical or phase 1) what the value of their assets are currently and how this will increase as they move through development. For most companies, there is a monetisation event in their minds and they are seeking to balance how far they take an asset through development to a point where they can license it, sell it or the business, or perhaps embark on an IPO. Clearly, they want to pick the optimum timing where risk and reward are favourable and an attractive market of partners or acquirers will be available. Conducting a valuation in such circumstances is usually relatively straight forward but there are many other factors that companies should consider.

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industry insight

The biotech renaissance
(c. 2013 ~ ?)

Summer Park
Business Development Director, PharmaVentures Ltd.

For the past few years, the biotech capital market has seen an unprecedented level of activity. Valuations soared, a record number of successful IPO's were completed and the end of the biotech ice age allowed investors and deal-makers to bloom. Optimists have called it the new beginning, and sceptics are labelling it another hyped bubble. So what does this all mean? Is the cash wave here to stay, or is it going to end as just another familiar story? Here is some insight from PharmaVentures.

More new businesses are emerging around the world than ever before. In the UK for example, there has been a 45% increase in the number of start-ups launched per year across all disciplines, since 2011[1] (*Figure 1*). Further characterisation of these start-ups shows that the number of these in the high-tech space has simultaneously increased by 31% in the last 5 years[2]. With record numbers of entrepreneurs in major markets outside the UK, such as the US[3] and China[4], there is a global cultural shift towards innovation and entrepreneurship.

The global bio-economy is no exception. It continues to grow, with scientists and entrepreneurs challenging industrial dogmas and translating cutting-edge technologies into innovative products. All with one simple vision: a better world. Biotech is a universal technology platform which is driving innovation across several sectors such as food technology, life sciences and renewable energy.

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1 Startup Britain, http://startupbritain.org/

2 Tech Monitor UK report by KPMG, https://home.kpmg.com/uk/en/home/insights/2014/07/techmonitoruk.html

3 Global Entrepreneurship Monitor, http://www.gemconsortium.org/

4 The Rise of Entrepreneurship in China, Forbes, http://www.forbes.com/sites/tseedward/2016/04/05/the-rise-of-entrepreneurship-in-china/#78bbc6086d61

New start-ups in the UK by year

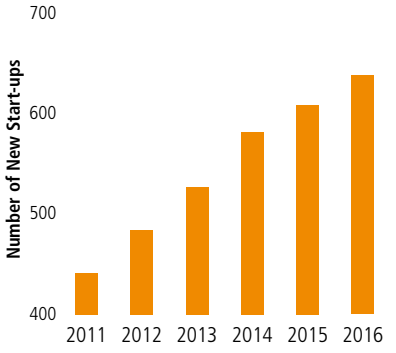

Figure 1 Source: Startup Britain, http://startupbritain.org/

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The biotech renaissance

Whilst Biotech may have multiple solutions within reach it is not without significant risk, and achieving its goals requires high levels of investment. Recently PharmaVentures interviewed Oliver Schacht, serial biotech entrepreneur and CEO of the Germany-based molecular diagnostics company Curetis, who gave his thoughts on this topic. Oliver explains that many biotech companies begin with a dream; to deliver a solution to some of the world's biggest problems. There is nothing wrong with setting a high bar in order to drive the business to success, however it is inevitable that a critical key component is access to money to turn this dream into a reality.

"It always takes longer, and always costs more. So raise as much as you can, when you can. Make sure that the company is well-funded to realise the dream and the vision."

Oliver Schacht
CEO of Curetis

In 2013, the capital market saw a very strong performance with 50 biotech IPOs, putting an end to the almost decade-long biotech IPO drought. This strong performance continued into 2014, during which 81 biotech IPOs raised $6.7b *(Figure 2)*.

Similarly, Innovation Capital – investment raised by companies with revenues of less than $500m – reached its height in the US and Europe. In 2015, biotechs around the world collectively raised $71b, with American and European companies claiming $41.3b – a figure that encompasses VC, IPO and almost all follow-on deals – of which $3.5b was raised through 235 Seed and Series A investment rounds. Interestingly, there was a high activity among biopharmaceutical corporate investors, such as Gilead, Celgene, Amgen and Biogen, which comprised the majority of the capital raised in the US[5]. The role of the corporate investor continues to be more important, both for the emerging companies as an alternative source of funds, and for the corporates to gain access to technologies and better deploy their capital.

The market simultaneously experienced higher levels of M&A and alliance deals, as the same optimism that lifted investment in biotech also encouraged vendors and buyers in the sector. In fact, Europe's larger biotech companies have demonstrated increased market values from 2011 to 2015, as a result of sustained commercial successes and growth via acquisition.

Despite such positivity, biotech's IPO momentum seems to have stuttered of late with conflicting views of the IPO window remaining open and for how long. The inflexion point was mid-2015. There are speculations that high-profile clinical trial and drug pricing issues had a negative effect on the sector's public perception, compounding the general volatility and macroeconomics of financial markets. However, thanks to the 2013-2015 record financing environment, biotech still remains well-funded despite recent fluctuations in the capital markets.

In the last few years biotech has seen a spillage of "innovation" to other key players in the ecosystem, such as biotech-specific incubators, risk sharing public-private partnership models, and "new world" investment vehicles. Examples include IndieBio, a specialist accelerator that exclusively invests in and helps grow synthetic biology start-ups and; Y Combinator – an IT incubator that started accepting biotech companies into its programmes in 2014.

JLINX is the latest in the Johnson & Johnson Innovation toolbox, designed to invest in and support the growth of biotech start-ups. In an **interview with PharmaVentures**, Kurt Hertogs (Head, Benelux and JLINX) explains the philosophy behind this new venture: to identify, invest in and nurture early-stage biotech companies and help advance their assets, without binding the founders into commercial rights and transaction obligations.

"We want to learn more about the opportunity and better understand the entrepreneur. The philosophy is that the entrepreneur should be free to make decisions for the best of their company."

Kurt Hertogs
Head of Benelux and JLINX

In Israel Johnson & Johnson Innovation has shown a completely different take on biotech incubation. Boasting the second highest number of NASDAQ-listed companies in the world, and 2015 alone showing 373 companies raising $3.58b and 69 companies being acquired for a total sum of $5.41b, Israel could be viewed as the world's "Start-up Nation." Israel's success in this area can be attributed in part, to the embrace of the public-private partnership. Technology Incubators are just one aspect of Israel's extensive suite of tech start-up support programmes, sponsored and funded by the Israeli government. FutuRx, partly owned by Johnson & Johnson Innovation, is one of these entities that are mandated by the Israeli government to actively identify, invest in and commercialise high tech IP. The key here is the government's heavy co-investment in every single one of FutuRx's deals. The rationale is for the public sector to take on as much investment risk, as early as possible, thus incentivising a continuous flow of cash into early-stage, high tech start-ups. This model continues to be embraced by countries around the world such as New Zealand and Argentina, that understand the impact it has created in Israel.

Many biotech start-ups have a global outlook from day one and need to be connected with their target markets. Having the right investors at the right time to facilitate this is crucial. Simon Haworth (Founder, Sino-UK Fund) is building a bridge between China and Europe through biotech investment. His goal is simple: to create a symbiosis between innovation-hungry Chinese investors, and biotech firms that are ready and relevant for the Chinese market. You can watch the **full interview with PharmaVentures** here.

"We have this bridge built between China and Europe, and it's a beautiful thing. It has seven lanes in both directions, there are no gates on either side anymore, but there are still only three cars on this bridge."

Simon Haworth
Founder of Sino-UK Fund

The past few years have witnessed a biotech renaissance. Reaching record financial performance and level of deal activities, companies of all shapes and sizes happily rode the buoyancy of the capital market. The time is now for biotechs to be tackling a different set of challenges. To achieve sustainable growth and continued innovation, particularly as the market shows signs of deceleration and the world is headed for even greater resource constraints. This long and hard journey will call for effective public policy and support from a well-informed public, but if history tells us anything in this sector, it is that biotech has weathered periods of uncertainty to return stronger each time.

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US and European Biotechnology IPOs by Year

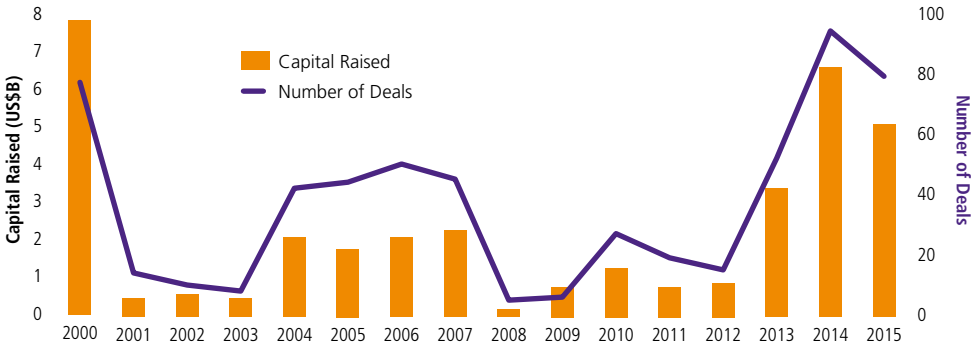

Figure 2

Source: EY, Capital IQ and VentureSource

5 Beyond borders, Ernst & Young

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Optimising the path to commercialisation

What do I need to know and when do I need to know it?

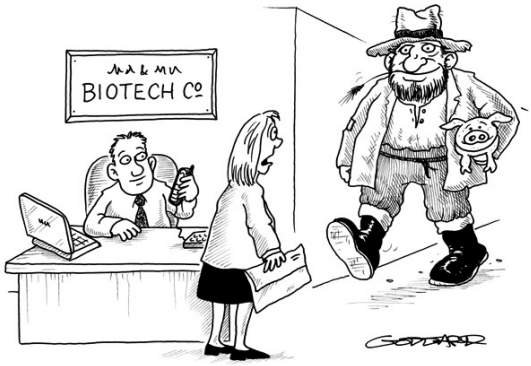
For many companies, and in particular smaller and emerging biotechs, the strategy seems pretty clear. Develop my asset to proof of concept and then seek a large partner to complete the expensive late stage clinical development and use their established sales and marketing infrastructure to maximise the returns. It is a tried, tested and successful model. The devil is in the detail, however, and decisions taken very early on often have a major impact upon the value and even commercial viability of an asset at the point at which it's time to do a deal.

When we are approached by a client for help in this area we undertake a thorough audit of the data and information the company has in hand already. It's not an absolute requirement to have all the boxes ticked but the more that remains for the commercialisation partner to do the greater the impact on the potential returns to the current owner. In times past one of the most important areas was to have a clear understanding of the regulatory path through development to approval. Larger companies were less concerned about areas such as pricing and reimbursement. Whilst the importance of regulatory considerations has not diminished, and if anything has increased in complexity, it is certainly true that an appreciation of the pricing and reimbursement position has become very important.

In expressing these views to younger biotech companies, we often hear agreement on the importance of these areas followed by the view that it makes sense to seriously consider them at or after Phase II when there is a much clearer picture of the safety and efficacy of the drug etc. and therefore how it stacks up against the competition. It is true that modelling the value of an asset can be done with a greater degree of certainty at this time but if the preclinical and clinical work up to this point has been done without regulatory, payer and prescribing practices taken into consideration you may find repeat work is required or the asset positioning is sub-optimal to deliver the best returns to both current owner and commercial partner. There are many assets competing for the attention and dollars of the big pharma companies, doing the right things at the right time is key to generating a compelling partnering proposition.

A Recent Case Study

PharmaVentures was approached by Biotech Company A who was developing a novel therapeutic for the treatment of Inflammatory Bowel Syndrome (IBS). The drug was at Phase I with excellent preclinical data including animal models and some limited clinical data on safety and efficacy. IBS is a complex condition, but a significant problem for a very large number of people of which the majority self-medicate and the rest seek medical intervention. Company A was keen to understand what the value of the asset would be at the end of Phase I (where they expected to have clear efficacy signals) and ready for Phase II and also at the end of Phase II. The outputs would help them make decisions around when to partner the asset.



"You know you said you wanted to partner with big pharma... ?"

IBS can take different forms featuring either constipation, diarrhoea or both along with pain, discomfort and bloating. Company A had data indicating they could impact upon all of these features which was ideal from a valuation perspective as it would potentially capture all patient sub-groups and thus maximise the value of the drug. In order for PharmaVentures to build an appropriate valuation model it was important to understand physician prescribing practices. This was accomplished by interviewing Key Opinion Leaders in the field. From the KOL studies it was clear that patients present with varying, and often multiple, IBS features but the physician will use the best treatment option available to resolve the most troublesome aspect in the first instance. The drugs available to the physician is dictated by those that are reimbursed and approved. In order to gain this status, the clinical trials that were undertaken needed to address endpoints that regulators could approve against and payers would be willing to reimburse. In the case of IBS, there are clinical guidelines developed by experts (Rome III and recently released Rome IV) for the treatment of the various forms of IBS. The guidelines are of extreme importance in clinical development and gaining regulatory approval, but less so in everyday clinical practice where the physician will seek the best option for the patient in front of them. We now start to see some of the issues emerging.

Start at the end and work back

As Company A knew their drug could impact on all aspects of IBS they were keen to include all patient types in their clinical development plan to maximise the asset value. An excellent strategy, but what, ultimately will be the label claim for the drug? One could envisage it involving "The treatment of IBS symptoms including diarrhoea, constipation, pain and bloating". But would the regulators allow such a claim? Furthermore, would the label claim influence how physicians prescribed the drug? Assuming these points can be addressed, what price could the drug command and would it be supported by the payers and reimbursers? It's clear that in order to develop a robust valuation model now, and have the right clinical development plans in place, the regulatory and payer considerations were important. All of the component parts are connected and influence each other. Knowledge of regulation, payers and prescriber practices all inform the development plan and valuation models which drive toward decisions and deal points. Making informed decisions based upon all the inputs even at this early development stage would give Company A the best chance of returning the highest value for their asset whilst spending their precious development dollars in the most efficient and effective way.

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IDT Australia completes initial CMAX transaction with I'rom Group

PharmaVentures is pleased to announce that it acted as adviser to IDT Australia Limited for the successful divestment of CMAX, a dedicated clinical trials business, to the Japanese healthcare company I'rom Group Co. Ltd. for a minimum AUD 14,000,000.

The acquisition has satisfied the conditions precedent, and as part of the agreed upon structure of the deal, IDT will receive the first tranche of AUD 10,000000. I'rom Group will now own 61% of the shares of the newly formed CMAX Clinical Research Pty Ltd. (CCR); and I'rom Group and IDT will jointly manage CCR through their 61% and 39% respective share holdings. This will allow I'rom Group to integrate the CMAX business and to learn from IDT's experience in managing CMAX, paving the way for I'rom Group to acquire the remaining shares of CCR over the next twelve months.

The remaining AUD 4,000,000 is guaranteed, but this may increase if CCR exceeds a revenue target for financial year 2017. A further payment could arise if CCR reaches a specific milestone before the close of financial year 2018.

Stephen Waterman, Managing Director, PharmaVentures said; "We are delighted to have used our expertise in the CRO sector to assist IDT in its strategic move into the specialty generics space."

Fintan Walton, Chairman and Chief Executive of PharmaVentures said: "This deal both establishes PharmaVentures as a player in the CRO M&A space as well as continuing to demonstrate its expertise in cross-border transactions in the Asia-Pacific region."

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Optimising the path to commercialisation

Who can help?

PharmaVentures has deep experience in commercialisation of assets and a good adviser knows what they don't know and where to access other expertise to complete the picture. In this instance, we engaged with Tony Mitchell of the regulatory consultancy S-Cubed and David Cotterell and Stephanie Bewick of Apex Healthcare Consulting for pricing and reimbursement expertise. Companies with early stage assets often delay seeking advice from both of these areas and then incur delays and additional cost later on when they find the clinical development they have conducted will not support regulatory approvals or a pricing and reimbursement strategy that delivers optimal value.

Tony Mitchell
S-Cubed

Expert regulatory input early in development is vital to ensure a product will meet regulatory requirements at all stages along the development pathway, from early proof of concept through to product registration. There are many regulatory guidelines which provide guidance along the way, but there are occasions when either a guideline does not exist, or it is simply not applicable to the product in question and cannot be followed. It is in this latter scenario that early engagement with a regulatory expert is critical to define the development plan and route to registration. This was exactly the situation facing Company A and their innovative product for IBS.

The regulatory guidelines for IBS categorise potential new therapies by subtype, which in turn defines the clinical trial patient population, study design features, and expected outcomes for registration of a new therapy. Recent regulatory approvals in the field of IBS have adhered to the guidance both in terms of patient population (Rome III criteria), disease sub-type (IBS-Constipation or IBS-Diarrhoea) and clinical study design features, including utilisation of pain and defecation abnormalities as primary endpoints.

The unique properties of Company A's drug, whilst potentially providing life-enhancing treatment for patients with the condition, were such that the standard IBS clinical development pathway as per the guidance and recent approval precedent, was not applicable. This was particularly evident for the patient population in which all IBS sub-types could potentially benefit, and should therefore comprise the clinical trial population. In addition, efficacy for this innovative treatment would most effectively be demonstrated using a primary endpoint for which there was no precedent or guideline rather than the conventional abdominal pain and defecation abnormalities endpoints.

Hence, the guideline could not be strictly followed and deviation would be necessary. This is generally permitted, as the purpose of any guidance is to assist with, rather than mandate, the development pathway for a product in a particular disease area. However, regulators do expect guidance to be followed unless there is a very good justification for not doing so. This is where regulatory advice is critical to assist Company A with their development plans, clinical study designs, justifications for deviation from the guidance, and subsequent consultations with the regulators in order to maximise the likelihood of regulatory acceptance and approval. Heading off down a path that deviates from guidelines and practice which is familiar to regulators could result in adverse regulatory responses and for the company, wasted time and additional costs to repeat clinical studies.

David Cotterell & Stephanie Bewick
Apex Healthcare Consulting

While it is obviously critical to gain regulatory approval, reimbursement coverage by healthcare payers is the final key hurdle. National, and in some cases, regional payers (in Europe) and the Managed Care Organisations (in the US) assess new products using a range of approaches often different to the regulatory authorities. Payers are focused on getting value for money and particularly in Europe, ensuring that new entrant product demonstrates improvements over existing treatment.

- In order to assess cost effectiveness and constrain free pricing, the G-BA in Germany conducts an early benefit assessment of new drugs. This allows the evaluation team to weigh up the product's benefits against a range of criteria, including quality of life. If a drug's only benefit is to improve quality of life, it is excluded from reimbursement, whereas innovative products for serious diseases with high unmet need are fully reimbursed. All other products are grouped into therapeutic categories which are allocated a group reference price. If the marketed price exceeds this reference price, the patient has to cover the outstanding amount as a co-payment.
- In France, in order for a drug to be reimbursed, it is evaluated by the Transparency Commission (Commission de la transparence (CT)) to assess its perceived medical benefit (SMR) as well as its improvement in medical benefit rating (ASMR), and given an SMR rating as well as a therapeutic value rating (ASMR 1-V). ASMR1 accounts for drugs which demonstrate a major improvement over standard of care and are reimbursed 100%; ASMR 2 is given to drugs showing a significant improvement over standard of care and is reimbursed 65%, and this continues down to ASMR 5, which are not reimbursed as they show no improvement. So although the French system does not control the price band, it controls the level of reimbursement, once a product is allocated a reimbursement band, the company then starts a price negotiation with the Comité Economique des Produits de Santé (CEPS)
- In the UK, NICE conducts a Health Technology Appraisal of products expected to have a significant health benefit, make a significant impact on other health-related government policies or have a significant impact on NHS resources.

An example of how a recent entrant of an IBS treatment was considered by payers is a useful yardstick for how Company A's product may be assessed.

- Linaclotide was the most recent entrant for IBS in 2013 and NICE did not consider it necessary to conduct a HTA based on the stated criteria, but the product was approved for reimbursement in refractory patients who have failed prior treatment, thus restricting its use on the NHS to this patient group.
- The G-BA in Germany conducted an early benefit assessment of linaclotide, but concluded that added benefit could not be demonstrated because comparator data as dietary advice in the trials was not tightly controlled.
- It is unclear if France has assessed linaclotide, but older anti-spasmodic products, when assessed where given a reimbursement level of 15% as standard of care is low priced.

A new product such as Company A's product, will have to demonstrate in comparative studies a clinically significant benefit over the comparator standard of care. The dietary advice in the trials will have to be very tightly controlled to ensure that the study arms are comparative. If a primary endpoint deviates from the accepted endpoints, i.e. bloating, it is likely that payers will require more than one primary endpoint to carry out their clinical and economic evaluation.

It will be important to engage with national payers early to understand the extent of the cost effectiveness data package requirement vs. standard of care. Early insight will give Company A the opportunity to marry this advice with the regulatory feedback to design appropriate clinical trials.

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conference update

J.P. Morgan 2017
9-13 January, San Francisco

Biotech & Money London
7-8 February, London

European Life Science CEO Forum
6-7 March, Zurich

Bio-Europe Spring
20-22 March, Barcelona

Anglonordic Biotech Conference
4 May, London

Biotrinity
8-10 May, London

BIO International Convention
19-22 June, San Diego

To meet with PharmaVentures' experts at any of these conferences, please contact Rachel Hampstead: rachel@pharmaventures.com

Or

To arrange an interview with PharmaTelevision, please contact Matt Royan: matt@pharmaventures.com