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PharmaVentures
Experts in deals and alliances

November 2013 Issue 9

Heads of Terms

Eliminating deal busters

In my experience, deal making is not for the faint hearted. Getting the deal done can be excruciatingly painful but it is exciting and the triumphs outstrip the despairs. The two key hurdles are alignment and the illusive 'skeletons in the closet'. Spotting them early is one of the things PharmaVentures do so that they can be dealt with on behalf of our clients.

Take alignment. Most would agree that alignment between buyer and seller is crucial and leads to enhanced chances of getting the deal done. There are several reasons for non-alignment; the common ones being price and strategic fit. However, often non-alignment resides amongst the stakeholders within the buyer or seller organisations and sometimes both! The three key stakeholders are senior executive management, the Board, and the shareholders. If they cannot be aligned sufficiently then the deal will either drag on or fail altogether. Non-alignment within the stakeholder groups themselves can be lethal, particularly if any are signatories to the deal! A mix of shareholder groups with different exit expectations is common and so are 'activist' minority shareholders wielding disproportionate influence. Identifying these early on or even testing to see if they are lying dormant is an essential activity before one embarks on the sale process. Once identified, if they can be dealt with in advance it can reap significant benefits, both financial and time wise.

Now let's look at 'skeletons in the closet'. It is amazing how many companies have issues that lie dormant for years and only come back to haunt them when it comes to a sale. Some of the biggest problems a seller will have arise from assumptions that such issues never existed, were dealt with appropriately in the past, or will be overlooked during due diligence. In our experience the forensic nature of due diligence usually means such items will be found or, if they do not come to light during pre-completion diligence, they will

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Why Nanoscale is a Big Deal!

21 years ago I met an innovative scientist at Porton Down called Dr Bob Carr. Bob showed me a rudimentary engineering set up comprising a laser, glass surface and a 20x standard microscope. Bob invited me to take a look at the specs of light dancing around on the surface - virus particles too small to be visible with a 20x standard microscope. Bob had invented something very interesting but what was the benefit beyond academic interest?

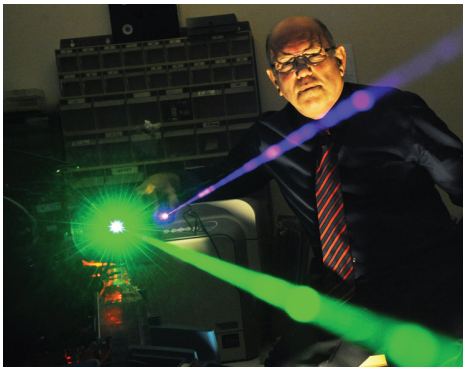
Fast forward to 2011 when I met CEO Jeremy Warren of NanoSight, a company that had, with minimal VC investment, grown from the seed of Bob's invention into a successful, growing company selling instrumentation and software into the physical analytical space, pharma/biotech and academia worldwide.

NanoSight realised they had reached a tipping point as the technology was maturing and going mainstream yet still had vast growth potential. They could have sought further investment and grown the business organically or looked for an acquirer with the means to take the business to the next level.

NanoSight chose the latter option but sought first, with PharmaVentures help, to understand the potential of the technology in the diagnostics space through their ability to count size and characterise exosomes (biological cellular messengers in health and disease) since publications had already shown that these could have massive potential in diagnostics and disease target identification.

PharmaVentures conducted a series of key opinion leader interviews to provide insight into how they would look at such a technology and if it represented something

Paul Walker and Duncan Roberts (both Malvern Instruments) with Bob Carr, Jeremy Warren and the rest of the NanoSight team.



of value to them. It was clear from this work that any subsequent M&A process should target the analytical companies that NanoSight were already very familiar with plus life science tools companies and diagnostics companies.

Another influencing factor that emerged was that M&A deals in the life science tools space generally occurred at higher multiples than in the pure analytical non-life science tools sector. Targeting both in a structured M&A process would be key to delivering competitive tension and the best return for NanoSight.

In the M&A process that followed, PharmaVentures targeted over 70 companies who best fit the profile of an ideal acquirer for NanoSight. Seven life science and non-life science research tools companies signed CDAs. Three were selected for further diligence and two were invited to submit best and final offers.

As a result, the acquisition of NanoSight by Spectris plc occurred on September 30, 2013, NanoSight becoming part of the Spectris company Malvern Instruments Ltd.

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conference update

- **JP Morgan Healthcare Conference 2014**
  32nd Annual J.P. Morgan Healthcare Conference
  January 13–16, 2014
  San Francisco, California

To meet with PharmaVentures' experts at this conference:
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Heads of Terms

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rear their heads post closure. Finding these 'skeletons' early in the preparation phase can make a huge difference to success. Most can be dealt with or disclosed early on in the sale process and even in the data room.

But even if you have addressed all the above to the satisfaction of both sides, don't assume it will all be plain sailing. Recently in gathering signatories of minority shareholders on a short form SPA, a client who had done the right preparatory work in locating all the shareholders and issuing advance warning that their signatures were required was stymied at the 11th hour by a shareholder who was taken so ill that they could not sign their name or issue verbal instruction for a third party to act on their behalf. Expect the unexpected and build in as much contingency as you can.

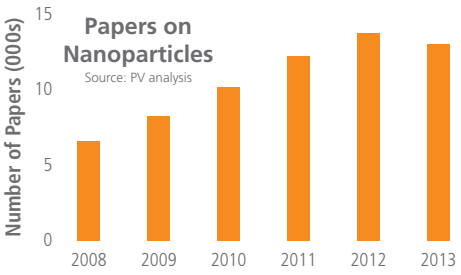
How can companies eliminate these potential hurdles to a deal? Through preparation! The most successful deals that we have been involved in are the ones where our client has prepared for sale. Clearing up alignment issues is crucial. Are senior executives aligned with the Board and shareholders? How are decisions going to be made by the buyer and the seller? Are the decision makers aligned? Additionally, going through what the buyer is looking for and thinking ahead of what is in the data room helps to unearth potential 'skeletons'. Finding these and dealing with them appropriately is essential to fruitful deal making. Preparation should be looked at as self-due-diligence, seeing things through the eyes of the buyer. That is where experienced advisors can help.

Dr Fintan Walton
Chief Executive,
PharmaVentures Ltd.

Nanotechnology to play an increasing role in Nanomedicine

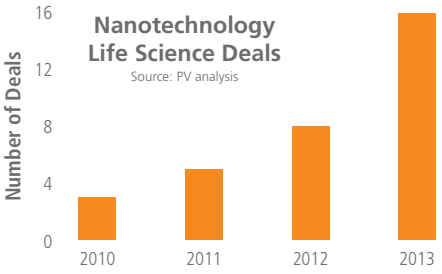
The term Nanotechnology refers to the domain of science and engineering that is applied to structures and materials that measure only a few billionths of a meter. The term was coined by Japanese scientist Norio Taniguchi almost 40 years ago, and then popularised by Eric Drexler in his "Engines of Creation: The Coming Era of Nanotechnology" in 1986. Over the next 20 years the convergence of experimental advances in manipulation of materials no bigger than the width of a DNA molecule facilitated the development of this field from the closed confines of leading research labs into the world of applications for the general public. At the beginning of this century President Clinton put a political seal of approval on the sector by announcing the U.S. National Nanotechnology Initiative (NNI). It is hard to believe the technology is almost 40 years old as it is only in the last 5-10 years that nanotechnology has found favour in commercially viable products. Among areas where it is having the most significant impact is medicine.

> *"We have been hearing about the promise of nanomedicine for a long time, but it is now really starting to move […]. There is a new level of confidence in this approach among the big pharmaceutical companies ... We will see more and more products in clinical testing over the next few years and I think that is very exciting".*
> (cit. Dan Peer, Nanomedicine Laboratory, Tel Aviv University).



Growth of publications in peer-reviewed journals is a good indicator of emerging fields and can give an early warning of the next big technology area that major players will look to exploit. Nanoparticle related publications over the last 5 years certainly indicate this and we are now experiencing its application in healthcare sectors such as drug delivery transitioning to the mainstream with big players such as Pfizer, AstraZeneca, Amgen and Sanofi entering the dealspace.

The global nanomedicine market is expected to reach over $100 billion by 2014 and is projected to grow at a CAGR of 12.6% over the period 2012-2016. Currently 250 "nano"-products are in use or being tested in humans. Nanomedicine products already on the market account for approximately 10% of pharma sales. The emergence of subsectors of nanotechnology such as nanorobotics and the development of new nanomaterials are among the key factors contributing to this market growth.



The spectrum of applications of nanomedicine is even wider and spans from drug delivery to imaging techniques, from diagnostic tools to active compounds and from medical devices to novel monitoring systems/approaches. Nanotechnology is accelerating rapid advances in areas such as genomics, combinatorial chemistry, high-throughput robotic screening, drug discovery, high-throughput sequencing, and bioinformatics.

The most prolific areas underpinned by nanotechnology advances are the pharmaceutical formulation field, reformulation and drug delivery. Reformulation is driven by the significant needs in cancer treatment where improvements in imaging contrast agents, biomarkers and diagnostics and highly targeted drugs with minimal impact on adjacent tissues and the overall patients' status are all eagerly being sought. Nanoparticle carriers and antibody-conjugated drugs are among the two most successful delivery strategies. The first nanoparticulate drug formulation, approved by the FDA in 1995, was a liposome-encapsulated formulation of the chemotherapeutic agent doxorubicin for treatment of Kaposi's sarcoma, a cancer often associated with AIDS.

Among some of the most exciting developments in drug delivery technologies are a temperature-controlled polymer that uses the DNA code to assemble itself into a structure capable of triggering the release of toxic cancer drugs (Syracuse University); the combination of mild heat and nanoparticle-delivered chemotherapy at Oregon State University; silicon "Nanocages" to carry protein-based drugs past the body's natural defences created by Researchers in Singapore; "Nanoviricides", made by polymeric lipids with a virus-binding ligand on the

surface, which trick viruses into attaching and infecting them, thus encapsulating the virus and preventing further infection (Connecticut-base nanotech company Nanoviricides); and also the nanopatch being developed at the University of Queensland and the hydrogels containing nanoparticles which improve topical delivery of drugs from Yale University. Currently there are 128 active clinical trials involving nanoparticles (www.clinicaltrials.gov).

Given all the activity in the nanomedicine sector, it is no surprise that we are now starting to see deals emerging between the pioneers and developers and the larger more established healthcare companies as they seek to scope out the landscape of patient treatments of the future.

Earlier this year, BIND Therapeutics, a privately held company developing targetable and programmable compounds based on a proprietary nano-platform, signed agreements with three global pharmaceutical companies, together worth nearly $1 billion. A $200 million (per drug) collaboration with Pfizer to develop targeted medicines, possibly for cancer treatment, a similar deal with AstraZeneca and a third one with Amgen, who agreed in January to pay up to $180.5 million for the right to develop cancer drugs using BIND's technology. BIND's proprietary Medicinal Nanoengineering platform is the result of research carried out at Robert Langer's laboratory at MIT, one of the pioneers of nanomedicine applications.

"*Anything you can do to improve targeting of tumours rather than normal tissue – whether that is through an armed antibody or nanoparticle approach – increases the chance of success*" said Susan Galbraith, who leads AstraZeneca's oncology research.

Another approach for drug delivery, using tiny particles of gold as drug carriers, is being explored in a deal that AstraZeneca signed in December 2012 with CytImmune.

One other area that is currently receiving a lot of attention is 3D printing. The technology advances that have allowed the miniaturisation of the printing components can be found within the research laboratories and associates of the founding fathers of Nanotechnology. Taking 3D printing beyond the realms of toys, figurines and popular consumer products, Prof. Chen's Nanoengineering group at University College San Diego has demonstrated the ability to print three-dimensional blood vessels in seconds. Organovo recently joined forces with Autodesk to focus on 3D printing of tissues and organs. At the Vienna University of Technology, after having optimised a "super-fast" nano-3D printer, scientists are now working on the development of bio-compatible resins to create scaffolds to which living cells can attach themselves, facilitating the systematic creation of biological tissues. In the near term, the most likely use for this technology is in drug testing, an $11 billion sub-segment of the Drug Discovery Technologies Market. This market alone is, forecast to soar to $79 billion by 2017 and tissue engineered therapies, an $11 billion market already.

It is worth noting that the growing nanomedicine industry requires the plethora of support and research technologies that facilitate front line medical breakthroughs in exactly the same way as conventional medicine. As such the life science tools sector is critical to nanomedicine development and the quality control of products it develops. Materials at the nanoscale can have different chemical, physical, or biological properties compared to their conventionally-scaled counterparts. Operating at the nanoscale can modify the previously known characteristics of a drug and this requires regulatory bodies such as the FDA and EMA to provide guidance for developers in this field. Such guidance is only possible if the tools are available to measure, count, characterise and monitor at the nanoscale. Companies operating in this research tools domain such as Malvern Instruments (recent acquirers of NanoSight), Izon, Thermofisher, FEI, Cameca and NT-MDT are poised to reap these benefits.

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meet the team

Alisa Selimovic

PhD
Business Analyst

Alisa has recently joined PharmaVentures, where she works with the Corporate Advisory Team as a Business Analyst. Alisa comes from an engineering background, with a double degree in Biomedical Engineering and Life Sciences from the Flinders University in South Australia. Her strong interest in the cardiovascular field led her to a DPhil in Biomedical Engineering at Oxford University as a Robert Menzies Memorial Scholar in Engineering, where she worked on the development of a computational model of cerebral aneurysm evolution. At Oxford, Alisa's interests transitioned from "bench-top science" to applying her skills in the healthcare business arena. Prior to joining PharmaVentures, Alisa has worked as a clinical engineer at the TORT Centre in Scotland, as Projects Officer for South Australia Pathology, and, while at Oxford, as a technology developer for a mobile smart water meter for use in rural developing communities.

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ESTEVE

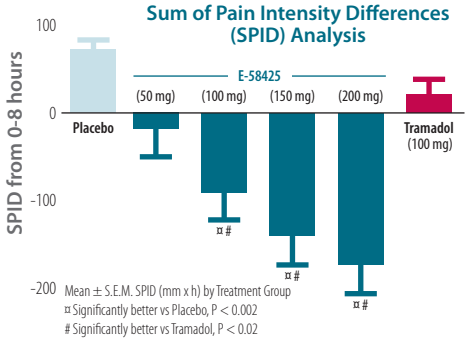
New Strategies for Established Drugs

Esteve has developed the world's first co-crystal drug containing two active pharmaceutical ingredients (APIs). The product, E-58425, is a novel, first-in-class, patented co-crystal of Celecoxib and Tramadol for the treatment of moderate to severe pain. E-58425 recently passed another development milestone with the successful completion of Phase II clinical trials.

In this randomised double blind, placebo controlled Phase II study involving 420 patients with acute post-operative moderate to severe pain following extraction of two or more impacted third molars requiring bone removal, E-58425 demonstrated superior efficacy and safety compared to both placebo and the current standard of care. The data confirms that co-crystallisation enables E-58425 to deliver synergistic efficacy whilst at the same time not potentiating the side effects of the constituent APIs. This is achieved by modulation of the pharmacokinetic properties of Tramadol and Celecoxib in the co-crystal such that they are distinct from those of the simple co-administration of the two individual APIs.

The study evaluated four dose strengths of E-58425 (50mg, 100mg, 150mg and 200mg) versus placebo or 100mg Tramadol. "All of the dosage strengths of E-58425 tested contained amounts of the individual APIs that would be considered sub-therapeutic in the moderate to severe pain model used," noted Mark Mayhew, head of R&D business strategy. The study demonstrated a faster onset of action, longer duration of analgesia, and less need for rescue medication with E-58425.

The results of the trial showed that the 100mg, 150mg and 200mg doses of E-58425 were associated with a dose dependent, significant and clinically relevant superior analgesic activity in the primary endpoint (sum of pain intensity differences at eight hours) versus placebo (p<0.002 for



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all three doses) and versus tramadol ($p<0.02$ for all three doses). The 50mg dose also did better than 100mg tramadol but the result was not statistically significant.

Regarding safety and tolerability, 50mg and 100mg doses of E-58425 showed a frequency of treatment emergent adverse events (TEAEs) very similar to placebo and importantly, E-58425 did not potentiate the development of those adverse events.

Overall E-58425 demonstrates clinically relevant and robust pain relief at low doses of E-58425 (hence low dose of each active ingredient) that are associated with a better safety and tolerability profile and improved risk-benefit ratio.

These results demonstrate the potential use for E-58425 in acute, moderate to severe pain; however, the strength of the results also suggest that E-58425 could be a very valuable new medicine for the treatment of chronic, moderate to severe pain.

Esteve is a leading pharmaceutical chemical group based in Barcelona (Spain) with significant international presence. Operating for over 84 years, the company focuses on innovative R&D of new medicines for unmet medical need. Esteve currently has a team of about 2500 professionals, and has subsidiaries and production facilities in several European countries, USA, China and Mexico.

In addition to E-58425, Esteve has a number of projects in different stages of development including those that target the Sigma-1 receptor. The most advanced project here is E-52862, which could be a novel approach and a new mechanism of action for pain. Additionally, E-52862 could have potential applications in other neurological and psychiatric indications.

PharmaVentures is currently assisting Esteve find partners to continue the clinical development of E-58425 in both acute and chronic moderate to severe pain.

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industry insight

Emerging Markets

Emerging Markets (EMs) are increasingly a key part of the growth strategy of many life science/ healthcare companies. For example, by 2020 over 90% of the growth in global pharmaceutical spend is projected to be from EMs. In healthcare overall, there is nearly a $1 trillion projected expansion of EM healthcare expenditure from 2013 to 2017. The drivers of this growth will bring considerable disruptive changes to all sectors of the healthcare industry, bringing opportunities and threats to healthcare firms. Companies will need to determine an overall strategy that plays to both Developed Markets (DMs) and EMs.

China is the most important EM market, accounting for over $410 billion of healthcare expenditure in 2012, of which $82 billion was pharmaceutical spend. The Chinese pharmaceutical market is projected to grow strongly, perhaps up to 20% per year over the next five years and account for about 25% or more of total worldwide pharmaceutical growth by 2017. Not surprisingly, all large pharma groups remain committed to China despite the challenges of doing business there and regulatory pricing pressures on selected drugs. According to Capital IQ, there were over 100 M&A transactions to date in 2013.

China, however, is not the only interesting EM story. For example, Latin America is an especially exciting region for healthcare investment. Average 2012 GDP per capita is over $10,000, nearly twice that of China. There are an estimated 200 million people in Latin America belonging to the 'Global Middle Class' defined as those earning $6,000 to $25,000 per year. This range is considered to be where people have sufficient financial security and disposable income to buy a variety of products and services, including healthcare. This Latin American Global Middle Class figure compares with approximately 175 million in China. Further, the region's demographics are favourable with a large, rising young population. Medium-term aggregate GDP growth is projected to be 5-7% per year with healthcare expenditure growth projected to be around 7-10%.

Not surprisingly, investment into Latin America is strong despite some near-term economic and political bumps. According to Capital IQ, there were over 35 healthcare acquisitions in Latin America to date in 2013 across a range of healthcare segments. A particularly notable transaction this year was the acquisition of Laboratorios Andrómaco S.A., a Chilean pharma company, by Grünenthal GmbH, the research-based German pharma company. Sanofi, Takeda, Celesio, Pfizer, among many others, have also made significant strategic acquisitions in Latin America.

Acquisitions of local players or joint ventures are the main ways to achieve scale or significantly expand in EMs. However, Western corporate development teams are often frustrated by how unstructured an M&A process can be in EMs on top of other considerations such as poor information (for due diligence), cultural sensitivities, unfamiliar jurisdictions and high valuation expectations. Local management and their respective advisors can lack the experience and familiarity of Western-style M&A processes and negotiation styles. The combination of these factors can lead to protracted processes and ultimately deals falling through.

Under these circumstances, PharmaVentures can provide crucial support in this process, to make the initiative much more effective and efficient. We can work with the acquirer's line management on the ground and put structure into the process so that internal M&A teams (at regional/global HQ) can execute the initiative efficiently. We can gather the difficult-to-obtain information as well as raise the quality of information obtained to help accurately and properly evaluate prospective acquisitions. We can be the primary driver of local due diligence. Finally, the value of an intermediary to facilitate the dialogue and process can help minimise tensions and preserve 'face', often aspects that are more important in many EMs than, say, in more direct Western ones when negotiating deals.

PharmaVentures is particularly active in Emerging Markets, advising companies and private equity firms in investment into all key EMs areas. We are familiar with the transaction environments in China, rest of Asia Pacific, Eastern Europe, MENA, Latin America and sub-Sahara Africa.

For a discussion on how we can help you in Emerging Markets, please contact:
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There had always been a good relationship between NanoSight and Malvern so why not just approach Spectris/Malvern and do a deal?

In this instance, where the technology had very wide appeal it was right to first understand the market and then use a professional M&A advisory firm to prosecute the deal process and expose the company to a wide scope of potential acquirers so NanoSight could achieve the best return for their shareholders.

In a recently interview with Jeremy Warren and Duncan Roberts (Business Development Director, Malvern), both discuss the integration of NanoSight into Malvern and how something at the Nanoscale will deliver big returns in the future.

http://www.pharmatelevision.com/Video/1151-PTVNewsReviewNanoSight.aspx

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