termsheet

PharmaVentures
Experts in deals and alliances

February 2014 Issue 10

Heads of Terms

2014 is going to be good?

Having returned last month from San Francisco, where the JP Morgan Healthcare Conference is held each year, I am pleased to feed back that the mood is the most positive for five years.

What is clear is that companies have finally got their act together; big pharma has had to change and restructure, a process that we at PharmaVentures have assisted in divestments. Although restructuring has been a painful process, we now have a healthier pharmaceutical industry emerging. While most of the pharmaceutical companies now have stronger pipelines, the search for late stage clinical programmes remain a challenge. Biotech, of course, has had a great boost from the IPO market and rise in stock prices in the USA and that has passed through into the rest of the biotech world so we see growing confidence there.

There is also a greater shift to the concept that therapeutic healthcare not only involves the use of drugs alone but can involve new exciting technologies emerging in materials, electronics and other physical sciences. There is a greater convergence of diagnostics and medical devices into the therapeutic space and this area will become transformative in 2014.

Emerging Markets remain a key challenge for established pharma companies. Although there has been a greater level of growth in those markets there is still a degree of uncertainty. During 2013 several companies faced challenges in countries like China and India and although the Brazilian economy has increased, it is beginning to slow down again. Recent volatile exchange rate fluctuations have not helped either. What is coming out of all this are new ways of thinking about how to operate within these countries including ways to work with local companies who are equally trying exploit the growth opportunity. As these emerging countries are coming under the influence of World Trade Organisation they realise that their future lies outside their own territories

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industry insight

Reducing Pain for Patients and Dealmakers

(Abridged version. Full white paper available for download)

Pain management

Pain management continues to face the dual hurdles of abuse of the most efficacious therapies and the difficulties of developing and commercialising new treatments. This challenging environment presents difficulties both for large pharmaceutical companies looking to bring new solutions to market and the mid size and smaller biotechs developing new approaches and seeking commercial partners.

Pain is heterogeneous with not only a sensory component, due to the stimulation of nociceptors, but also an emotional one. Consequently there is significant variability in how patients perceive and describe pain. Absence of objectivity and the strong connection with underlying conditions make pain management and pain therapeutic development a complex task for physicians and drug companies. So much so, that a number of major pharmaceutical companies have de-prioritised pain in their R&D pipelines.

Pain is classified as acute, chronic, and neuropathic (associated with a functional abnormality of the nervous system).

A treatment guideline, "the pain ladder" has been designed by the WHO to assist specialists in the prescription of analgesic drugs.

The pain ladder also advocates a multimodal approach involving the combination of drugs with different MoAs. Evidence shows that when multimodal analgesia is employed, smaller quantities of drugs are needed and thus side effects reduced.

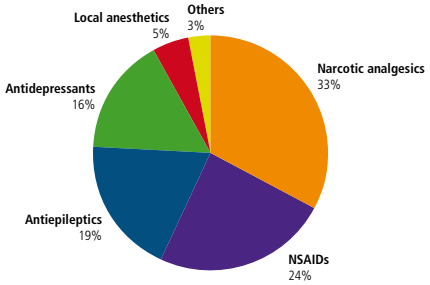
Market overview

The pain market can be sub-divided into therapeutics and medical devices.

The pain therapeutics market reached $28.6B in 2010 and will rise to $35.1B (3% CAGR) by 2017. Growth is driven by aging populations with increased incidence of pain associated conditions and increased demand in markets such as Japan.

NSAIDs hold the largest market share but the dominance will be threatened as Pfizer's Celebrex comes off patent later this year. Acetaminophen is forecast to grow at a CAGR of 3.1% to 2016, driving sales of non-narcotic analgesics as the number of product combinations which include this API increases.

Pain management therapeutics by class



Narcotics make up approximately one third of the global market with the top three narcotics (2012) being OxyContin (37%), Duragesic (fentanyl) and Nucynta (tapentadol).

A pure number count of development stage assets looks reasonably healthy. However, this hides the reality that the majority of these assets are reformulations and recombination products. Beyond this there is renewed interest in biologics (anti-NGF) which were halted in 2010 but have recently re-entered the clinic. The limitations of the therapeutic approach leaves a significant unmet need in pain management which many are seeking to address with medical devices. Devices have the advantage of being quicker to develop and more amenable to continuous improvement at relatively low cost/risk. The pain management devices market was valued at $2B (2012) and is expected to grow at a CAGR of 13.1% to reach $5B by 2018. Among the most exciting/innovative FDA premarket approvals in 2013 is a device for migraine; eNeura's Cerena Transcranial Magnetic Stimulator (TMS).

USA Vs Europe: prescription paradigms and regulations

A key consideration for businesses commercialising pain management products is significant inter and intra-market variability. While the USA and EU combined represent over 80% of the global market, they have major differences in the general approach to pain management, resulting in marked different prescribing practices.

Historically, the approach to analgesics and narcotics in the USA has been quite relaxed, with limited regulations. This resulted in prescriptions almost doubling in the last 10 years despite no change in the overall prevalence of patient-reported pain. Over-prescription of opioids and poor control over refills fuelled abuse and addiction to these

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so opportunities for them to expand are on the rise.

At the end of last year I visited Australia and New Zealand where the key issue still remains the ability to raise money. Australian companies have, however, adapted to the local investment environment, including the Australian ASX stock exchange, by developing lower risk and quicker to market products, particularly in the area of medical devices. These are the companies that are doing well. Furthermore, a number of Australian biotech companies carrying the traditional higher risk drug development route have moved out of Australia to the USA to seek investment and to exploit the potential to list on NASDAQ. For example, Biota who were once listed on the ASX are now listed on NASDAQ.

As a natural optimist I genuinely believe that 2014 is going to be a really good transformative year!!

Dr Fintan Walton
Chief Executive,
PharmaVentures Ltd.

conference update

The Pharma Summit 2014

13 March 2014, The Dorchester, London, UK

In its 20th year, The Pharma Summit is established as the major industry event that brings together all major stakeholders - industry leaders, policy-makers, regulators, academics, scientists and patient representatives, innovators from IT and biotechnology as well as from frontier markets, to tackle the most pressing issues the industry is facing and to assess the power of a range of disruptive new business models.

http://www.economistinsights.com/healthcare/event/pharma-summit-2014

BIO-Europe Spring 2014

10-12 March 2014, Turin, Italy

BIO-Europe Spring® is the springtime counterpart to EBD Group's flagship conference, BIO-Europe®, and continues the tradition of providing life science companies with high calibre partnering opportunities.

http://www.ebdgroup.com/bes/index.php

To meet with PharmaVentures' experts at any of these conferences please contact Dr Adrian Dawkes, Vice President adrian.dawkes@pharmaventures.com

industry insight

Reducing Pain ... *continued from front page*

drugs. Opioid dependence greatly impacts the US economy costing approximately $56B per year.

Under pressure from Congress, patient groups, and the American Pain Society the FDA has taken a number of measures to reduce opioid addiction. Schedule II drugs can only be dispensed through a physician's written prescription and no refills are allowed.

The FDA initiated action in 2009 when they made it clear that it would be incumbent upon manufacturers of high-potency opioids to implement risk evaluation and mitigation strategies (REMS) by early 2012.

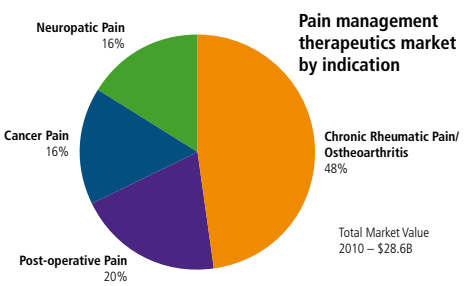
In April 2013, the FDA banned generics of OxyContin because the risk of abuse greatly outweighed the benefits. At the same time the FDA gave Purdue the right to put a specific claim on its abuse-deterrent OxyContin formulation.

In May 2013, the FDA announced that the development of abuse-deterrent opioid analgesics was a public health priority and issued an abuse-deterrent guidance document.

Shortly after the release of this document the FDA approved Zohydro ER (Zogenix), the first single-entity extended-release hydrocodone product for the management of severe round-the-clock pain. Despite a negative (11-2) vote by an expert panel the high dose (50 mg) was approved without abuse-deterrent features, sparking significant reaction. In November 2013 Zogenix announced a $250M agreement with Altus therapeutics to develop an abuse-deterrent formulation of Zohydro.

The climate of uncertainty over tougher rules for prescription of opioids and the growing concerns related to addiction and side-effects has had an effect in the treatment paradigm in Europe where caution and a fear of duplicating the issues seen in the USA has resulted in under-prescription of opioids.

European physicians prefer to prescribe high dosages of NSAIDs and weak opioids for acute pain, whereas strong opioids are mostly dispensed in a hospital setting for post-operative and traumatic pain. Across Europe, chronic pain patients are mainly prescribed NSAIDs. The pain landscape is thus very varied with Europe and the USA having very different drivers and dynamics. As a result pharma companies need different strategies in terms of market access and product release, which has an impact on portfolio management decisions, new product development and deal making activity.



Development pipeline and trends

Over 200 companies have drugs in their pipelines with over 400 drugs in the clinic, almost 150 in preclinical stage and 70 research programs with a 50/50 split between narcotic and non-narcotic therapeutics. Of these, the vast majority are oral formulations, with about 50 injectables and the same number between trasmucosal, transdermal and topic.

The FDA pronouncements and long-standing challenges of this sector has seen dealmaking continue to decline from its peak in 2011. Abuse deterrence has fuelled a boost in reformulation based deals as technology solutions come to the fore. Alongside abuse deterrence we see novel reformulation approaches such as Esteve's Tramadol/Celcoxib co-crystal technology which, if subsequent clinical data supports, will deliver better analgesia with lower dosing and side effects.

Notable deals include:

- Danish biotech Egalet collaboration with Japanese pharma Shionogi to develop abuse-resistant hydrocodone opioid therapeutics.
- Australian specialty pharma QRx entered a collaboration agreement with CMO Aesica for the worldwide promotion of the company's abuse-deterrence technology Stealth Beadlets™.
- AcelRx and Grunenthal entered a licensing agreement in 2013 for Zalviso, a drug-device combination product which allows controlled delivery/administration of a proprietary sublingual tablet formulation of sufentanil.
- In July 2013, Australian biotechnology company Bionomics announced the signature of a $172M 2-year collaboration deal with Merck & Co to use its ionX drug discovery platform and MultiCore chemistry to discover and develop novel small molecule candidates for the treatment of chronic and neuropathic pain.
- The biggest value deal during 2013 saw Lilly and Pfizer agree on a co-development and licensing deal for a monoclonal antibody to treat neuropathic pain. The high-risk anti-nerve growth factor (NGF) pain drug tanezumab is expected to be launched in 2015 and reach sales of $88M by 2018.

A divergent territorial deal trend is apparent from 2009 to 2013. The uncertain and increasingly strictly regulated USA market

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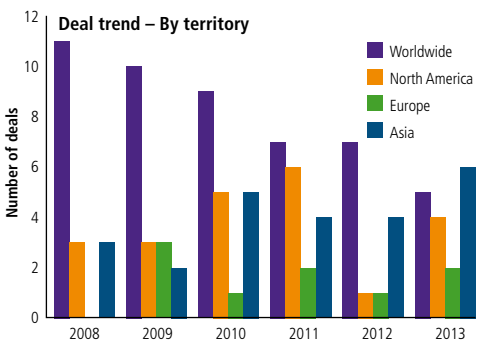


Why Size and Timing Matter

Nigel R Trim, Consultant to PharmaVentures CRO Practice

It is easy to find trading and M&A multiples for mid and top tier CROs as their financial data are plentiful. Although consolidation in this sector is often dramatic and draws the attention of the entire industry, we should not lose sight of what is happening lower down the food chain, amongst companies that will form the next generation of mid-tier CROs and where data are much less available and value more variable.

Global R&D spend is likely to be $60BN in 2014, with 37% outsourced and the lion's share in phase II-IV (>$15BN). The top 10 CROs account for 75% of this $15BN, leaving mid to low tier CROs with approximately $3.75BN to share. The market is projected to show year on year growth of 8%. So why is it that so many small to medium CROs fail to maintain this growth performance?

We frequently see the growth profile of CROs adopting a sigmoid curve, an initial lag phase is superseded by rapid, sometimes exponential growth and ultimately this gives way to a period of deceleration and in many cases we find companies that have reached their natural ceiling and "flatline".

The micro-CRO territory, companies of less than 50 employees, is built on long-term relationships with particular clients or specialisation in therapeutic areas or geography. These businesses are typically more aligned with resourcing than CRO and there is little pressure to truly deliver "Full Service". It is an area where multiple suppliers are acceptable to a client in the conduct of a single study and overall contract values are correspondingly low. They are, however, the primordial soup of the industry and it is the ambitions and subsequent growth of these companies that facilitate consolidation.

The true mid-tier is a challenging environment and companies are required to profitably sustain and develop a much larger organisational structure, requiring ever greater contract values. There are pressures to globalise and truly provide "Full Service" whilst at the same time be able to provide expert local advice even in complex areas such as regulatory. In an environment where clients deem it increasingly unacceptable for mid-tier CROs to subcontract service elements, the negative effects of pressure to employ every specialty in-house has been amplified by the large CROs lowering their sights as the markets drew breath in 2009-12.

Flatlining

When thinking about the maintenance of growth rates, it is worth considering the causes of flatlining:

Geographical

Geographical profile can restrict growth. This may be due to specialisation in a specific country or group of countries. A CRO may take a significant market share of any one area and find itself protecting its market rather than developing it. The fortunes of a country's internal market can influence the available domestic business as has been seen in some southern European countries over the last few years. Political instability or changes in legislation can also affect specific countries; an extreme example would be the ban on the export of clinical trial samples by the Russian Federation in May 2007.

Therapeutic

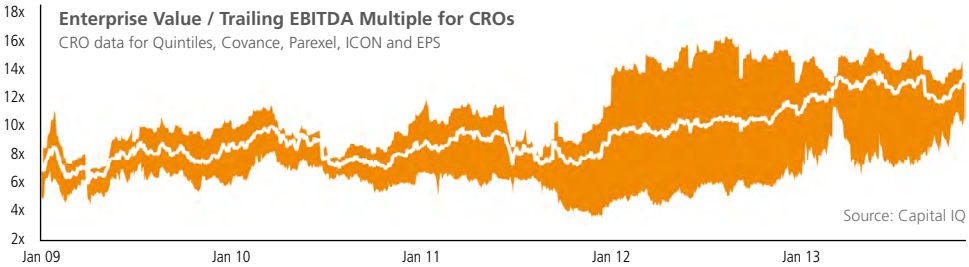
Therapeutic expertise is often used as a differentiator by CROs who specialise in specific areas such as dermatology or ophthalmology. Whilst these companies are developing their therapeutic expertise, their focus will win business, however, it can ultimately become restrictive and it may be difficult to expand outside it specialties.

Infrastructure/process

CROs run according to a set of metrics, and there is a formula for profitability. With growth, there is the potential for exceeding the capacity of their processes which will require re-engineering to accommodate a further growth phase including restructuring management and information systems, adding further service capability and capacity to the business. The stall point for some companies is where this re-engineering does not happen and business development becomes unable to convince clients of the enhanced service capability.

Organic growth

Organic growth is usually achieved either by conducting more studies or studies of greater complexity or size. The dollar value of each piece of work is the most important and whilst it can result in client concentration issues, it will ultimately fuel faster organic growth. The converse is also true; a business failing to increase the dollar value of each contract will find development an uphill battle and is more likely to flatline.



Enterprise Value / Trailing EBITDA Multiple for CROs
CRO data for Quintiles, Covance, Parexel, ICON and EPS

M&A resistance

The concept of an M&A programme causes nervousness even amongst seasoned business principals. Those who have created profitable, established businesses struggle with valuations of their own businesses, businesses they are acquiring or businesses that may be acquiring them. There is a lack of clarity on how to value their businesses, as often high EBIT multiples are presented which then fall away during ensuing discussions. For many, it will be the first time they have experienced the possibility of buying and selling businesses and the result can be indecision about the most advantageous time to engage.

Investment

Investment to fund organic growth and the accompanying internal re-engineering is difficult to procure as the returns for an investor are difficult to communicate compared to funding for an M&A programme, where the uplift in the value of combined businesses is more apparent.

Satisfaction

For private, individually owned companies it may simply be that the business owners are satisfied with their performance; the company is delivering the results they require in return for an acceptable level of input from them. For them to move the business on through its natural ceiling involves an unacceptable level of risk.

M&A valuations significantly influenced by size

At PharmaVentures, we are active in several CRO transactions on both the buy-side and the sell-side. The graph below illustrates our experience that there is a steady progression in M&A valuation multiples as a CRO increases in size, reflecting an overall improvement in quality of the acquired business (eg. broad spread of clients and revenue streams, institutionalisation, management team, etc.). It is evident from this that owners of CROs need to consider aspects of their business that may need to be developed to ensure the value of their company is optimised.

Many business owners conclude that the best route out of a flatline is to sell. Whilst the consolidation market is vibrant with companies looking to acquire EU CROs of all sizes and specialisations the most important consideration is when to sell. For business owners the greatest temptation is to continue surfing the growth wave until it subsides leaving them with a static business. We feel that the optimum time to sell is usually towards the end of the exponential growth phase. At this stage the business is successful, energised, has a good track record and can legitimately project strong future growth. Identification of this "time to sell" requires vision and maximising the value proposition requires preparation. In the micro/low mid-tier CRO sector this will usually involve stripping cost and removing any lifestyle factors. Several attributes influence the final value of a business, one of the most significant being the

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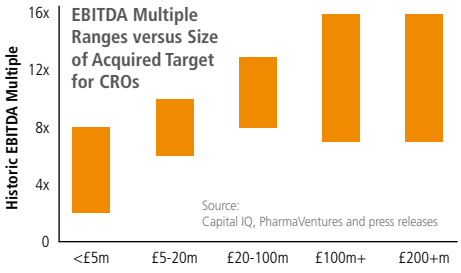
industry insight

Size and timing ... continued from page 3



reliance on the Principals for stability, specific knowledge and client relationships. A business with a knowledgeable, stable and empowered management team will always be more appealing to an acquiring company than one that relies primarily on its owners. Transparency and credibility are also key. Projections from flatlining companies showing sudden unsubstantiated growth or expansion plans are an inherently harder sell than presenting the strengths of a business such as reputation, niche service, therapeutic or geographic performance.

Finally, business owners should each consider the outcome they require M&A. The path for a non-participating shareholder is straightforward but owners are frequently pivotal to the business. There are decisions to be made based on the career and lifestyle aspirations of the vendors, all of which can influence the deal structure. Even with clear succession planning, business owners who are critical to the business are often required to stay with the business for several years after sale. Therefore, business owners should enter an M&A process with vision, planning and a clear definition of success.

For more information on PharmaVentures work in the CRO space please contact
Dr Stephen Waterman, Vice President
stephen.waterman@pharmaventures.com

Download the full white paper:
http://www.pharmaventures.com/content/cro-whitepaper

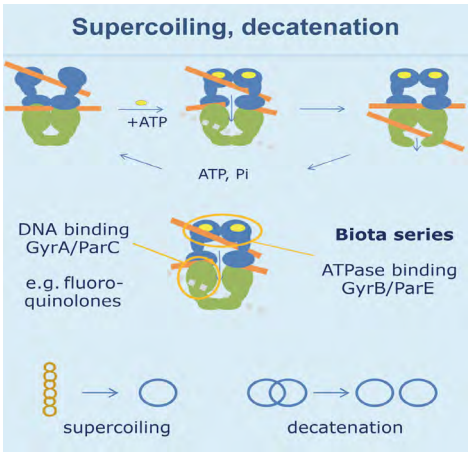
featured client

Novel DNA Supercoiling Inhibitors for the Treatment of Drug-resistant Bacterial Infections

Following a strategic decision to focus on clinical stage programs, Biota is seeking to divest its research stage antibacterial assets which include a preclinical candidate for drug resistant Gram-positive infections and an advanced lead for drug resistant Gram-negative infections.

biota

Biota's DNA supercoiling inhibitor compounds dual target the ATPase activity of two heterotetrameric enzyme complexes, DNA gyrase and topoisomerase IV. These essential, highly conserved bacterial enzymes have no human homologues and by targeting both enzymes, the frequency of resistance is extremely low. Inhibiting the ATPase activity represents a novel mechanism of action, distinct from the fluoroquinolones which target the DNA binding activity of the complex.



Attributes of antibacterial assets

- **Novel** class of **small-molecule** antibacterials
- Dual-targeting of the **clinically unexploited** GyrB and ParE subunits of DNA gyrase and topoisomerase IV
- **No pre-existing resistance** in contemporary clinical isolates
- A **low resistance frequency** and low propensity for the development of resistance
- **Bactericidal** activity against a broad range of bacteria
- Active against **drug-resistant** strains of Gram-positive and Gram-negative species
- Good bioavailability with potential for **intravenous** and **oral** administration
- **Efficacious** in multiple rodent models of **Gram-positive** and **Gram-negative** infections
- Chemically **tractable** and **scalable** synthetic routes, with an attractive **safety** profile
- **Comprehensive patent estate** covering major commercial markets, **solely owned** by Biota
- Long potential period of **market exclusivity**

For a non-confidential teaser:
http://www.pharmaventures.com/content/novel-dna-supercoiling-inhibitors

Biota is open to a range of potential deal structures including full acquisition, license or spin-out.

Biota Pharmaceuticals, Inc. is focused on the discovery and development of anti-infective products to prevent and treat a number of serious and potentially life-threatening infectious diseases and has discovered two generations of neuraminidase inhibitors (NIs) that have been commercialised.

Biota also has two Phase II clinical-stage product candidates; laninamivir octanoate and vapendavir, a potent, oral broad-spectrum capsid inhibitor of human rhinovirus (HRV).

For detailed information::
Dr Kate Moore, Senior Director
kate.moore@pharmaventures.com
+44 1865 332713 or +44 7960 508429

industry insight

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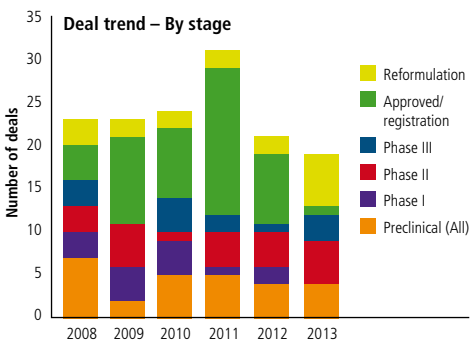
coupled with differential physician approaches elsewhere is shifting dealmaking away from worldwide deals to more regional, fragmented ones, aimed at finding the right partner and strategy for a specific regulatory environment.

2013 deal numbers saw a further decline in addition to the 30% decrease between 2011 and 2012. On the contrary, the average deal value increased from 2012 to 2013, going from $219M to $275M. Analysts are positive regarding the deal environment for 2014.



M&A is set to increase materially in 2014 with TEVA acquiring NuPathe, the owner of the first FDA approved anti-migraine patch, for $144M. There is still significant unmet need in many parts of the world, with the penetration of narcotics in certain countries at single digit levels. Chronic pain patient care is probably the bigger opportunity with tens of millions of people currently undertreated for pain.

Futher information:
Elena Lovo PhD, Advisor, PharmaVentures
elena.lovo@pharmaventures.com

Download the full white paper:
www.pharmaventures.com/content/reducing-pain-patients-and-dealmakers

forthcoming events

Further details of these conferences on page 2

To meet with PharmaVentures' experts at either of these conferences please contact
Dr Adrian Dawkes, Vice President
adrian.dawkes@pharmaventures.com