

Key Deals

Top deals this month in order of reported value

Mylan Laboratories and **Merck KGaA** have signed a definitive agreement under which Mylan will acquire 100% of the shares of the various businesses comprising Merck Generics for an all-cash consideration of **€4.9 B** (US\$6.6 B) (Deal no. 27219).

Potential deal value: US\$6.6 B.

Bausch & Lomb (B&L) has entered into a definitive merger agreement with affiliates of **Warburg Pincus**, a private equity firm, in a transaction valued at approximately US\$4.5 B, including about US\$830 M of debt. Warburg will acquire all of B&L's outstanding shares (Deal no. 27253).

Potential deal value: US\$4.5 B.

Actavis has received a takeover bid from **Novator**, an investment firm led by the Chairman of Actavis, Bjorgolfur Thor Bjorgolfsson, for US\$2.749 B. Bjorgolfsson plans to privatise Actavis, with the aim of enabling it to be a greater risk taker (Deal no. 27202).

Potential deal value: US\$2.749 B.

Bristol-Myers Squibb (BMS) and **Pfizer** are to enter into a worldwide collaboration to develop and commercialise apixaban, an anticoagulant discovered by BMS that is being studied for the prevention and treatment of a broad range of venous and arterial thrombotic conditions. The deal includes an upfront payment of **US\$250 M** and up to **US\$750 M** in milestones (Deal no. 27087).

Potential deal value: US\$1 B.

New York University (NYU) has sold a portion of its worldwide royalty interest in Remicade® (infliximab) to **Royalty Pharma**. NYU will receive US\$650 M in cash upfront plus additional payments should yearly sales of Remicade exceed certain agreed sales hurdles (Deal no. 27153).

Potential deal value: US\$650 M.

Features

AstraZeneca and MedImmune:

A Match Made in Biologics Heaven? Page 5

Biologics have rapidly established themselves as 'the next big thing', and the relative sparseness of viable target companies has pushed acquisition premiums to new highs, as the major global players compete to buy a future stake in the biologics arena. The latest acquisition is that of MedImmune by AstraZeneca for US\$15.6 B. This article explores the rationale behind the deal and asks why it was that AstraZeneca was willing to go the extra mile for MedImmune.

Novartis Acquires Rights to Cytos'

Anti-Smoking Vaccine Page 9

This feature discusses the recent US\$497 M licensing deal between Cytos Biotechnology and Novartis for CYT002-NicQb, a therapeutic vaccine in Phase II trials for the treatment of nicotine addiction. The article puts the deal into the context of the current smoking cessation market and explores the strategy and rationale behind it.

How Companies Source their Licensing

Opportunities, Part I Page 12

As the pace of drug development within the biotechnology industry continues to accelerate, there is an increasing need to find partners for developing and marketing these drugs. To examine the challenges of this process, PharmaVentures has conducted a survey of company executives involved in sourcing licensing opportunities. In this two-part article, we present the results. In Part I, we show that there is a strong desire to optimise the licensing process across the industry.

Therapy Focus:

Anaemia in Chronic Kidney Disease and Cancer Page 16

Millions of cancer patients, and those suffering from kidney disease, develop anaemia as a result of a loss of the hormone erythropoietin (EPO). Treatment currently consists of regular injections of recombinant EPOs, with the market dominated by Amgen's Aranesp® and Epogen®, and Johnson & Johnson's Procrit®/Eprex®. However the market's biggest ever shake-up is on the horizon.

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Business Commentary

Pricing Drugs

Drug prices are a contentious issue, and one that will not go away. It appears inevitable that the pressure to reduce the price of drugs will come from all governments. Of course, the cost of getting a drug to market is getting costlier as regulatory bodies, correctly, demand more efficacious and safer therapeutics – and even when a drug is approved and on the market, additional monitoring of that drug is increasingly being required. Furthermore, the cost of manufacturing effective drugs, such as biologics, places upward pressure on prices. This means that, if anything, the price of drugs will continue to rise rather than decline. So what is the solution? For too long, we, as an industry – and that includes biotechs, pharmas and government regulatory bodies – have focused on the development of better and more effective drugs, and not on the means to improve the way we test them. If drugs could be proven to be clinically efficacious and safe sooner, and with smaller and faster clinical trial requirements, their prices would drop considerably. This is a huge challenge: the key question is, who should fund and develop these improvements? Whatever the approach, the process would need to be done in close consultation with government regulatory bodies.

“If drugs could be proven to be clinically efficacious and safe sooner, with smaller and faster clinical trial requirements, their prices would drop considerably. This is a huge challenge, and the key question is: who should fund and develop these improvements?”

There are already some initiatives, for example, the European Commission (EC) has proposed a partnership called the Innovative Medicines Initiative (IMI) with the European Federation of Pharmaceutical Industry and Associations (EFPIA). A precursor to the IMI was the InnoMed Integrated Research project under the EU Sixth Research Framework Programme for Research, Technological Development and Demonstration (FP6). InnoMed can be considered a pilot project for the IMI, which is part of the EC's proposal for the Seventh Framework Programme on Research and Technological Development. InnoMed's wide consortium base is being led by EFPIA and comprises 16 large pharmaceutical companies co-operating with 14 universities and eight small/medium-sized enterprises. IMI's key objective will be to tackle bottlenecks in the drug discovery process. For more information on this initiative go to www.imi-europe.org

A key component of all of this is our basic understanding of disease mechanism, so fundamental research is another crucial aspect in the drive to improve drug discovery processes, rather than just the discovery of new drugs itself. Worldwide, in proportion to GDP, the US is still the biggest contributor to publicly funded health R&D. It is no surprise, therefore, that it has the highest density of biotech companies. In the future, will it also be the biggest contributor to improving the efficiency of clinical trials and, thereby, allow drug prices to drop? And, in the end, it will be biotechnology research that will drive the price of drugs down, although this will require considerable spend on disease R&D, as well as co-operation between the different stakeholders, to make it all happen. Clearly, this is an area for publicly sponsored initiatives.

Fintan Walton

Chief Executive Officer

PharmaVentures Ltd

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AstraZeneca and MedImmune: A Match Made in Biologics Heaven?

As everyone now knows, biologics have rapidly established themselves as ‘the next big thing’, in the search for blockbuster wonder drugs, and everyone wants in, period. This, coupled with the recent boom in vaccine sales in response to the ever-present threat from pandemic influenza and the usual tail of ‘dwindling pipelines and shareholder pressure’, has driven global pharmaceutical companies into a frenzy of biotech acquisitions in recent years. As one might imagine, the relative sparseness of viable target companies has pushed the premiums to new highs, as the major global players compete to buy a future stake in the biologics arena. The latest addition to the list of independent companies to have succumbed to shareholder pressure and cashed in on the current semi-desperation of big pharma is **MedImmune**, which, subject to shareholder take-up, agreed on the 23 April 2007 to be acquired by global giant **AstraZeneca**, in a deal worth a massive US\$15.6 B (Deal no. 27024). As often accompanies such a high-figure deal, there has been much outcry as to whether or not this value is appropriate and whether the need to succeed has pushed the price too high? This article explores the rationale behind the deal in order to provide an insight into why AstraZeneca was willing to go the extra mile for MedImmune.

Takeover Target

MedImmune is a US-based, publicly traded biotech company, which operates primarily within the antiviral anti-infective and vaccines space. It has enjoyed success with its lead marketed product, Synagis® (palivizumab), a humanised monoclonal antibody used to prevent RSV in infants at high risk of developing an infection, which achieved blockbuster status with US\$1.1 B sales in 2005 and again in 2006. However, MedImmune has been less successful with another of its marketed products, FluMist®, an intranasal influenza vaccine, which has failed to deliver on the high level of sales that the company had hoped it would achieve, particularly in the wake of the pandemic influenza threat. In addition, the lack of sales growth for Synagis between 2005 and 2006, and failure to meet analyst estimates for both Synagis and FluMist sales in 2006, left the company in a weaker than expected state at the beginning of 2007.

The overall performance of the company in recent years has also resulted in some shareholder unrest. David Katz, President of **Matrix Asset Advisors**, which holds around 1.65 million shares in MedImmune, had petitioned the Board to sell the company on a number of occasions since the end of 2006. In response, MedImmune’s management declared that, having reviewed the current situation, it would continue to aggressively pursue its ongoing business plan and remain independent. It later came to light that billionaire investor and frequent shareholder activist Carl Icahn had declared a 1.16% stake in MedImmune in February 2007, and had subsequently threatened to nominate a slate of opposing Directors unless MedImmune’s Board put the company up for sale, because of what Mr Icahn considered to be lacklustre and suboptimal management. Although neither Katz nor Icahn held a particularly significant stake in the company, this kind of negative publicity can have a profound effect on other shareholders’ perception, pervading the generalised ownership and causing major headaches for the individuals trying to run the company.

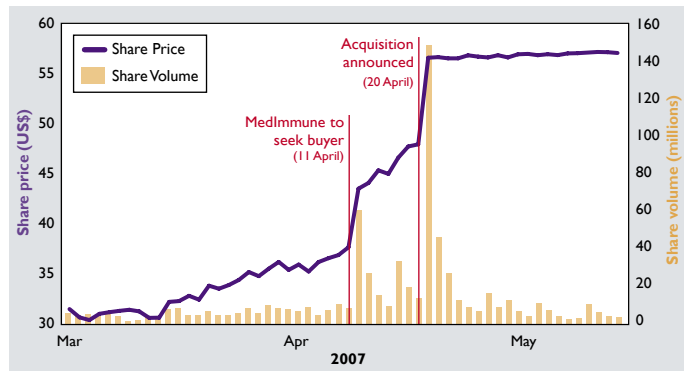


Figure 1 – MedImmune’s closing share price on Nasdaq in the period preceding and following announcement of its acquisition by AstraZeneca.

These incidents further supported the long-standing opinion within the investor community in general that MedImmune was a prime target for acquisition. So it came as little surprise when, on 12 April 2007, it was announced that the Board of Directors had authorised management to evaluate potential buyers in order to seek acquisition terms that would provide suitable value for shareholders. The motivation behind the decision was cited as interest from a number of major pharmaceutical companies and recent shareholder dissatisfaction. The immediate result was a 15% jump in MedImmune’s share price (Figure 1). Interestingly, MedImmune retained the services of **Goldman, Sachs** to assist in the process – a company which holds an 11% stake in MedImmune and is, as such, well motivated to find a buyer.

To say that MedImmune was in a favourable position to be acquired would be something of an understatement, given the current hunger of big pharma for biotech companies and their technologies. Since the beginning of 2005, of the US\$81 B that has been spent by global pharmaceutical companies on M&A, just under half has been spent on acquiring biotechs in order to expand into the vaccines and biologics arena (Figure 2). Prime examples of willingness to pay include the US\$1.4 B acquisition of **ID Biomedical** by **GlaxoSmithKline** (GSK), the US\$5.1 B acquisition of **Chiron** by **Novartis**, and the US\$13.3 B acquisition of **Serono** by **Merck KGaA** (Deal nos. 21591, 22116 and 25251).

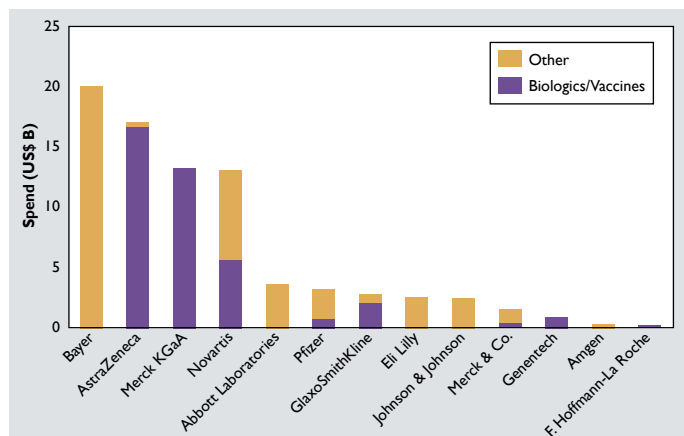


Figure 2 – The spend of global pharmaceutical companies on company acquisitions in the period 2005–2007 (Source: PharmaDeals® Agreements).

It is tempting to speculate, since MedImmune had stated that it had received interest from a number of major pharmaceutical companies, just which of these had been in the running. Unsurprisingly, the list is likely to have featured only top 10 pharmas, as they are really the only ones with the financial weight to compete at this level. However, with this in mind, Merck KGaA was able to find the means to buy Serono in the wake of its failed attempt to acquire **Schering**, indicating that non-top-tier companies could have made a bid in an attempt to make a step up the ladder. However, it would not be unreasonable to suggest that GSK and **Pfizer** could have put in bids. GSK already has successes in vaccines and respiratory medicine, and would have had the rationale to increase its presence in these fields, especially as it had previously shown some commitment to building a biologics business through the acquisition of **Domantis** for US\$454 M in December 2006 (Deal no. 25980). Similarly, Pfizer's recent purchases of **Bioren**, **Rinat Neuroscience** and **PowderMed** show commitment to biologics and vaccines (Deal nos. 21395, 23901 and 25502), and the impending Lipitor® (atorvastatin) patent-loss crisis could have provided the motivation to increase its pipeline through further acquisitions. When the chips were down though, it was AstraZeneca that emerged victorious, having sealed the deal with a massive US\$15.6 B dollar bid. This announcement sent MedImmune's share price up by a further 17.8% (Figure 1), but resulted in a 4% drop in AstraZeneca's, as investors failed to see the immediate value of the deal.

Evolving Strategy

AstraZeneca is going through a period of change, implementing a new strategic approach, and refocusing its R&D and externalisation efforts to meet the demands of the current global market-place.¹ Yet despite its best efforts, its late-stage pipeline remains relatively weak, having suffered from a string of failures over the last 2 years. In February 2006, AstraZeneca decided to withdraw its anticoagulant Exanta® (melagatran/ximelagatran), from the market owing to potential risk of liver side-effects. In May of the same year, the company discontinued the development of Galida™ (tesaglitazar), following safety concerns identified in Phase III trials. Further disappointment followed in October 2006, when the results of a Phase III trial for the ischaemic stroke drug Cerovive® (NXY-059) failed to demonstrate efficacy, ending both the development of the drug and the partnership with **Renovis** (Deal no. 12931). Most recently, AstraZeneca's and **AtheroGenics**' anti-inflammatory cardiovascular product, AGI-1067, failed to deliver in Phase III trials; here, again, the partnership dissolved along with the considerable hopes of blockbuster returns that AstraZeneca had had for the drug (Deal no. 22987). Termination of the partnership was announced on the 23 April 2007, the same day as the acquisition of MedImmune, perhaps in the hope that attention would be diverted away from yet another failure.

Although AstraZeneca was keen to state that its latest purchase was part of its ongoing strategic evolution, it is unlikely that the move to acquire MedImmune was an original part of any long-term plan. The high price, and relative speed at which the deal was drafted, indicate strongly that AstraZeneca saw this as an opportunity not to be missed and that it was going to do whatever it took to seal the agreement. Under the terms of the deal, AstraZeneca has agreed to acquire all of the fully diluted shares of MedImmune common stock at a price of US\$58 per share, a 53.3% premium over the share price on 11 April 2007, the day that MedImmune declared its intent to seek a buyer.

¹ PharmaDeals Review 81, March 2007, pages 5-7.

² Source: Evaluate Pharma®.

The acquisition is subject to tender of the majority of the outstanding MedImmune shares on a fully diluted basis, and the offer for these will close in June 2007.

Shortly following the announcement of the deal, an outcry began from shareholders and investor analysts alike, with all parties questioning the value of the acquisition to the future earning potential of AstraZeneca. From a different angle, on 16 May 2007, a MedImmune shareholder filed a class-action suit against the company, its executives and its Directors, claiming that the deal unfairly benefits them more than it does the public shareholders. It is easy to see why some shareholders may have been upset, with President and CEO David Mott set to receive somewhere in the region of US\$287 M, in return for the 2% stake he holds in the company. Other executives will also receive smaller, but similarly substantial, payments. AstraZeneca has stated that it remains confident that the deal will progress to completion, despite the ongoing legal sideshow.

One suspects that a company as well versed in the ways of business as AstraZeneca would not enter into such a deal if the executives in the driving seat did not have a fairly high degree of certainty that the company would reap substantial rewards during the lifetime of their own tenure, particularly given the current trend to oust underperforming senior executives. So wherein does the real value of the deal lie? This question is best addressed by breaking it down into a number of different components and assessing the relative value that each has to offer AstraZeneca's future revenue streams.

Marketed Value

The easiest place to look for value in the deal is in the direct revenue streams from MedImmune's currently marketed products. MedImmune's sales revenues in 1991 were US\$6 M, based on sales of CytoGam® cytomegalovirus (CMV) immune globulin intravenous for the prevention of CMV infection following organ transplants, a drug that was sold to **ZLB Behring** (of **CSL**) in 2006 for US\$120 M (Deal no. 25770). Since then, sales have grown to over US\$2.1 B in 2006, predominantly from sales of Synagis (Figure 3). Combined revenues from all of MedImmune's marketed products have been forecast to be worth around US\$9.5 B over the next 6 years.² This excludes the royalties that MedImmune is receiving from sales of **Merck & Co.**'s HPV vaccine Gardasil® (quadrivalent HPV vaccine), which, with an estimated royalty rate of around 7%, could be as much as US\$955 M over the next 6 years.² This royalty stream is the result of a deal between GSK and Merck & Co. in 2005 (Deal no. 19230), in which the two companies entered into a cross-licensing agreement to in order to settle patent rights relating to the development of and HPV vaccine: GSK had obtained the technology as part of a collaboration

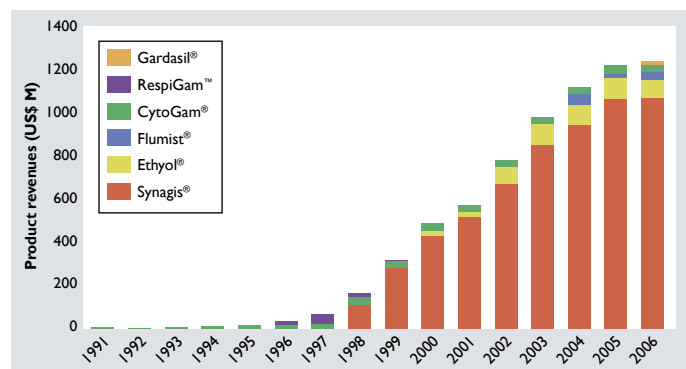


Figure 3 – MedImmune's product revenues in the period 1991 to 2006

(Source: Evaluate Pharma®).

with MedImmune (Deal no. 02048); and Merck & Co. had obtained it from CSL and the **University of Queensland** (Deal no. 16438). MedImmune will also receive royalties from sales of GSK's and MedImmune's vaccine Cervarix[®], another HPV vaccine for cervical cancer, which is aimed to hit the market later in 2007;³ assuming similar royalty rates to the Gardasil deal, this could send around US\$600 M MedImmune's way over the next 6 years.² However, given that MedImmune licensed its HPV vaccine technology from **Deutsches Krebsforschungszentrum** (the German Cancer Center), and is bound to pay a royalty stream to that body, this will reduce the actual amount that ends up in AstraZeneca's pockets (Deal no. 00291). In a recent analyst presentation, AstraZeneca indicated that, in much the same way that the company disposed of the Humira[®] (adalimumab) royalty stream to part-pay for the acquisition of **Cambridge Antibody Technology** (CAT) in 2006 (Deal nos. 25652 and 24261), it would consider disposing of the HPV vaccine royalty streams, if it were to receive the right offer.

The future revenue streams from FluMist are somewhat less significant, with less-than-successful sales figures now overshadowed by US FDA concerns over wheezing side-effects in very young children, a patient group for which MedImmune is trying to get approval of the vaccine. MedImmune invested a significant amount in acquiring FluMist through the US\$1.5 B purchase of **Aviron** in 2001 (Deal no. 09404), and then in spending further capital to reacquire the rights from Aviron's development partner **Wyeth** in 2004 (Deal no. 03631), so is likely to have been disappointed in its returns and in its failure to capitalise fully on the recent government stockpiling efforts as part of the global influenza preparedness plan. AstraZeneca may have looked with more favour upon MedImmune's second-generation FluMist, its Cold-Adapted influenza Vaccine Trivalent (CAIV-T), which has the advantage of being able to be refrigerated rather than frozen (as FluMist has to be). AstraZeneca may also have considered more favourably the revenue streams that MedImmune may receive from the outlicensing of its influenza reverse genetic IP to CSL and **sanofi-pasteur** (of **sanofi-aventis**), in deals signed in December 2006 and March 2007, respectively (Deal nos. 26090 and 26890). Additionally, in May 2006, MedImmune won a 5-year contract from the US **Department of Health and Human Services** (HHS), worth US\$170 M, to develop cell-based influenza vaccines (Deal no. 24234).

By far the biggest source of near-term revenues from the acquisition will come from sales of Synagis. In recent years, MedImmune made moves to reacquire exclusive rights for the US from its marketing partner **Abbott Laboratories** (Deal no. 02094), presumably in the expectation that the previous market growth of Synagis would continue (Figure 3). While sales growth from 2005 to 2006 was disappointing (almost nil), first quarter 2007 results are more promising, with revenues up by 9% over the same quarter in 2006,

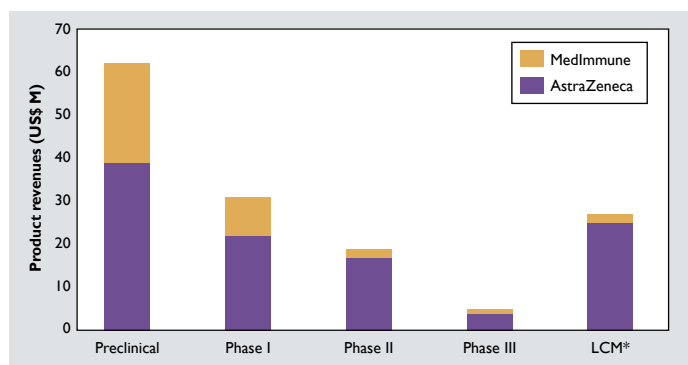


Figure 4 – Combined pipeline for AstraZeneca and MedImmune (Source: AstraZeneca).
*Life Cycle Management products

increasing from US\$463 M to US\$507 M. Although the patent on Synagis is not due to expire until 2015, the company has already taken steps to secure its place in the market with the development of its second-generation version of Synagis, Numax[™]. Originally developed in collaboration with **Applied Molecular Evolution** (AME) (Deal no. 08851), the product is currently in Phase III development, and has demonstrated significant improvements over Synagis.

Pipeline Possibilities?

At first glance, MedImmune's pipeline appears impressive, encompassing, as it does, a total of 34 products in development (Table 1). In comparison, Serono only had 16 compounds in clinical trials when it was acquired by Merck KGaA for US\$13.3 B in September 2006 (Deal no. 25251). However, although the acquisition of MedImmune does provide a number of additions to AstraZeneca's pipeline, the majority of these are at the early clinical or preclinical stages of development, and do not appear to relieve any of the pressure that AstraZeneca currently has on its late-stage pipeline (Figure 4). AstraZeneca has indicated that it expects three to five Phase II products to progress into pivotal Phase III trials in 2009/10, with key Phase II data expected during 2007/8. This should go at least some way to show shareholders that a future supply of new drugs is in the making, but may do little to quell any immediate fears. The trade-off is that the MedImmune pipeline consists almost exclusively of biologics and vaccines, thus allowing AstraZeneca to gain an immediate further foothold in this area of therapeutics, to beyond that which it attained through its acquisition of CAT.

The acquisition of MedImmune adds two Phase II products: an Epstein Barr virus vaccine that MedImmune has developed internally, and an anti-IL-9 antibody to treat asthma, which it developed through its collaborations with AME, and with **Geniera** (Deal no. 07844). Other clinical-stage products include MEDI-545, an anti-interferon (IFN) alpha antibody for the treatment of systemic lupus erythematosus (SLE), developed with **Medarex** (Deal no. 18508), and anti-CD19-BiTE[®] (MT103) for the treatment of various types of cancer, developed with **Micromet** (Deal no. 13022). MedImmune also has a combination vaccine that targets RSV and parainfluenzavirus (PIV)-3, which is currently in Phase I trials, and if successful, could prove to be a blockbuster drug, although history is littered with failed attempts to devise a vaccine for RSV. While AstraZeneca has rebuffed suggestions that it will seek to sell off any of the vaccines post-integration – hoping instead to generate significant royalty streams from at least two of the products – it is relatively difficult to see significant inherent value in the MedImmune pipeline, another reason why shareholders may have been uneasy and were keen to seek an exit while the market for acquiring biotech companies was good.

Success through Synergy

The true driver behind the deal with MedImmune, and the key reason that AstraZeneca was willing to pay over the odds, is the potential synergies that the company should be able to create through the combination of CAT and MedImmune. The acquisition of MedImmune allows AstraZeneca to immediately build an integrated biologics business that should greatly accelerate the discovery and development of new drugs, and catapults the company into a strong position for future growth, ahead of many of its competitors. The potential synergies derive largely from the combination of CAT's drug discovery platform with MedImmune's drug development

³ See Deal Tracker, page 15.

	Product	Indication(s)	Development status
Infectious diseases	Synagis® (palivizumab)	Respiratory syncytial virus (RSV)	Launched
	Flumist® (influenza virus vaccine live, intranasal)	Influenza virus	Launched
	CAIV-T	Influenza virus	Phase III
	Numax® (motavizumab)	RSV	Phase III
	EBV vaccine	Epstein Barr virus	Phase II
	RSV/PIV-3 vaccine	RSV, parainfluenza virus type 3 (PIV-3)	Phase I
	Pneumococcal vaccine	<i>Streptococcus pneumoniae</i>	Phase I
	H5N1 influenza vaccine	Influenza virus	Phase I
	hMPV/PIV-3 vaccine	Human metapneumovirus (hMPV)/PIV-3	Preclinical
	hMPV MAb and vaccine	hMPV	Preclinical
	Anti-RSV drug	RSV	Preclinical
	Anti-staph HP Mab	<i>Staphylococcus</i> spp.	Preclinical
	Third-generation anti-RSV MAb	RSV	Preclinical
Cancer	Ethylol® (amifostine)	Cytoprotective agent for cancer radio/chemotherapy	Launched
	Cervarix® (MEDI 517) ^a	HPV vaccine for prevention of cervical cancer	Preregistration
	Siplizumab (MEDI-507)	T-cell lymphoma	Phase I
	IPI-504 (Hsp90 inhibitor)	Multiple myeloma, gastrointestinal stromal tumours (GIST), non-small-cell lung cancer (NSCLC)	Phase I
	MEDI 538 (anti-CD19 BiTE®)	Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia	Phase I
	Anti-EphA2 BiTE MAb and conjugate	Cancer	Preclinical
	Hedgehog pathway inhibitor	Cancer	Preclinical
	Listeria-EphA2 vaccine	Cancer	Preclinical
	Anti-EphA4 MAb	Cancer	Preclinical
	Anti-EphB4 & EphrinB2 MAbs	Solid tumours	Preclinical
	Anti-CD19/20/22 MAbs	Cancer	Preclinical
	Anti-ALK MAb	Solid tumours	Preclinical
	Anti-cMet Avimer™	Cancer	Preclinical
Inflammatory diseases	MEDI 528 (Anti-IL-9 MAb)	Asthma	Phase II
	MEDI 545 (Anti-IFN alpha MAb)	Psoriasis, systemic lupus erythematosus (SLE)	Phase I
	BIW 8405 (Anti-IL-5R MAb)	Asthma	Phase I
	MEDI 546 (Anti-IFNα MAb)	SLE	Preclinical
	Anti-HMGB-1 MAb	Inflammation, septic shock	Preclinical
	Anti-ICOS MAb	Inflammation	Preclinical
	Anti-CD19, CD20 & CD22 MAbs	Autoimmune disease	Preclinical
	Anti-chitinase MAb	Cancer, inflammatory and respiratory disorders	Preclinical

■ biologic ■ small molecule ■ vaccine
^a In development with GlaxoSmithKline; see Deal Tracker, page 15.

Table 1 – MedImmune's product portfolio and pipeline (Source: MedImmune's website).

and manufacturing capabilities, and should provide synergies in a number of key areas. Two of these come from the additional R&D capabilities that MedImmune brings with it. First, AstraZeneca has implemented a staff retention initiative in order to ensure that the expertise that MedImmune's employees possess be transferred as part of the acquisition package; the AstraZeneca executives stressed the importance of the people as a key part of the deal. Second, the integration of MedImmune and CAT now provides AstraZeneca with the means and know-how to screen its repository of potential disease targets using small molecules, vaccines and

biologics, thereby increasing the options available for producing the most clinically valuable and marketable products. A third key aspect is the manufacturing capabilities that MedImmune possesses. AstraZeneca had previously been committed to spending around US\$1 B on building new manufacturing facilities in order to capitalise on its acquisition of CAT. Here, MedImmune's recently expanded manufacturing facilities, and the US HHS contract to develop cell-based influenza vaccine production facilities, meet all of AstraZeneca's needs for the immediate and mid-term future, with the option to increase facilities through modest investment, should it be warranted.

Verdict

There are a number of factors which are likely to leave many people in doubt as to the wisdom behind the decision to buy MedImmune. In response to the negative sentiment of shareholders and analysts alike, AstraZeneca was quick to defend the deal but was unequivocal in asserting that it did not expect to see a financial return until at least 2009. Given that AstraZeneca does not expect to launch any new products until at least 2008, and given its recent poor track record in taking products all the way to market, it is difficult to see where, in the interim period, the company is going to obtain its next shareholder-appealing win. Combine this with the facts that (i) the acquisition is being funded through a banking facility requiring AstraZeneca to take on permanent debt, (ii) the company is due to make around US\$3.3 B of payments in 2008 to Merck & Co. relating to the dissolution of the 1998 **Astra Merck** joint venture (Deal no. 02799), and (iii) the company has reaffirmed its commitment to its US\$4 B share buy-back programme, and you are left feeling that maybe AstraZeneca has taken on a little too much risk in order to build its biologics business. The inevitable drain on funds also means that AstraZeneca is likely to have to cut back on its externalisation activities, reducing the number of in-licensing and product acquisition deals it may be able to do, further emphasising a reliance on its current, albeit newly expanded, pipeline.

Another source of potential concern is the recent rumblings about the high treatment cost for biologics in general, indicating strongly that future pricing and reimbursement for these types of therapeutics will be much lower than at present, thus significantly reducing the potential profits that AstraZeneca may be able to generate with some of the products it is hoping to launch in forthcoming years. Furthermore, the pressure to provide biologics at lower prices is also likely to help push through legislation that will make it easier for generics companies to produce bioequivalents, so further cutting the returns that biologics will be able to provide.

As was mentioned previously, AstraZeneca will not have entered into this deal without fully exploring the risks it was about to take, but one has to question whether the opportunity to accelerate its biologics business through the acquisition of MedImmune has tempted the company to go too far and risk its long-term stability. Although it posted first quarter 2007 sales figures of US\$6.966 B, a 9% increase over those in the first quarter of 2006, it would not be outside the realms of possibility to foresee a future in which an overstretched AstraZeneca strays into the cross-hairs of another big pharma company, and find itself on the auction block (although its substantial permanent debt may act as a deterrent). However, this is doubtful, and the Board and Executive Management are more than likely to continue to display strategic flexibility and find ways to ensure that AstraZeneca will continue to prosper, and deliver high-quality medicines and more-than-welcome share dividends for years to come.

Novartis Gains Cytos' Anti-Smoking Vaccine

In April 2007, **Cytos Biotechnology**, a Swiss company engaged in the development of a new class of biopharmaceuticals (Text Box), entered into an agreement with **Novartis** for CYT002-NicQb, a therapeutic vaccine in Phase II clinical development for the treatment of nicotine addiction (Deal no. 27078). Under the terms of the agreement, Novartis receives worldwide exclusive rights for the vaccine and is responsible for late-stage clinical development, manufacturing and commercialisation. In return, Cytos is eligible to receive up to CHF600 M (US\$497 M) in the form of a CHF35 M (US\$29 M) upfront payment and potential development, regulatory and sales milestones based on the successful development and commercialisation of the vaccine. In addition, Cytos will receive royalty payments on net sales of products. Following the announcement of the deal, Cytos' share price on the Swiss stock exchange rose 5.4% to CHF175 (Figure 1).

The Smoking Cessation Market

According to the World Health Organization (WHO), smoking is the single biggest preventable cause of death, with tobacco claiming 4.9 million lives a year worldwide. There are an estimated 1.3 billion smokers, and half of them (some 650 million people) are expected to die prematurely of a tobacco-related disease. At the current rate of increase, the number of smokers will rise to 1.7 billion by 2025.

CYTOS

Cytos Biotechnology is a public Swiss biotechnology company engaged in the discovery, development and commercialisation of a new class of biopharmaceutical products: Immunodrugs™. Immunodrugs are intended for use in the treatment and prevention of common chronic diseases which afflict millions of people worldwide. The drugs offer the possibility of active immunisation with a highly immunogenic and completely defined product. They enable the induction of antibodies against disease-related molecules, and activation of appropriate T-cell responses directed against particular molecules (e.g. tumour and viral antigens) or modulation of certain disease processes (e.g. allergy).

Apart from CYT002-NicQb, Cytos has six other vaccines in clinical development for the treatment of allergy and asthma, Alzheimer's disease, hypertension, atopic dermatitis, melanoma and psoriasis. The Immunodrug programme in Alzheimer's disease, like the CYT002-NicQb programme, is partnered with **Novartis**, following a licensing deal in September 2003 (Deal no. 14591). This deal developed from an earlier collaboration between the companies that was announced in October 2001, and concerned the vaccine therapy CAD106, which is now in Phase I trials.

Cytos also has a number of preclinical Immunodrug programmes for diseases such as atherosclerosis, rheumatoid arthritis, multiple sclerosis and HIV. The company has stated that its business strategy is to partner selectively certain of its Immunodrug projects, after clinical proof-of-concept, with pharmaceutical and biotech companies, while fully developing other Immunodrug projects in selected niche areas and aiming to build its own marketing infrastructure.

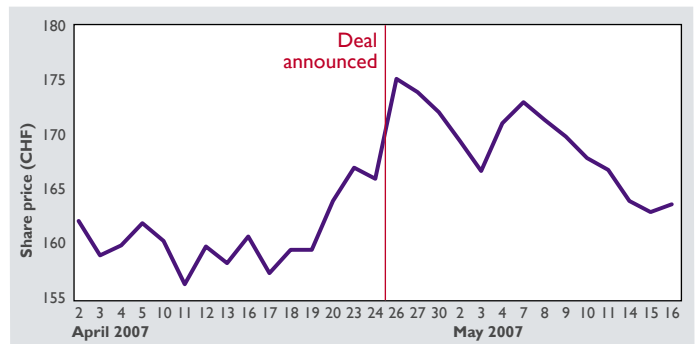


Figure 1 – Cytos Biotechnology's closing share price on the Swiss stock exchange in the days surrounding announcement of its deal with Novartis on 25 April 2007.

Growing health awareness, combined with restrictions on smoking in an increasing number of countries worldwide, has boosted the market potential for anti-smoking products. Nicotine replacement therapies are the main aids for smoking cessation, and include gums, lozenges, nasal sprays and inhalers that allow patients to actively control their nicotine dosage, alleviating withdrawal symptoms. **GlaxoSmithKline** (GSK) has a large share of the worldwide smoking cessation market with its NicoDerm® CQ® products (also marketed as NiQuitin CQ® and Nicabate CQ®), which had worldwide sales of US\$442 M in 2006, and its Nicorette® range, which had 2006 worldwide sales of US\$208 M. Novartis is also a major player in the nicotine replacement therapy market with its Nicotinell® products (also marketed as Habitrol®), which had worldwide sales of US\$220 M in 2006.

However, although nearly 75% of US smokers report that they want to quit, less than 5% of those who make an attempt are able to stay tobacco free for more than 3 months (*US Centers for Disease Control and Prevention, 2004 Surgeon General's Report*). CYT002-NicQb is designed to help prevent this relapse by reducing the reward-inducing stimulus of nicotine. The therapeutic vaccine is based on Cytos' Immunodrug™ platform, and vaccination with CYT002-NicQb has been shown to induce nicotine-specific antibodies that bind nicotine in the bloodstream. As the nicotine-antibody complex is too large to cross the blood-brain barrier, nicotine uptake into the brain, and the subsequent stimulation of nicotine-responsive nerve cells, is believed to be significantly reduced. Phase I and II clinical trials have demonstrated that CYT002-NicQb has a favourable safety profile and is generally well tolerated. In those patients who showed a high antibody response following vaccination, 57% demonstrated continuous abstinence for smoking between weeks 8 and 24 following treatment, compared with 31% who received a placebo.

The Competition

Smoking cessation products are becoming more innovative as drug developers move away from simple nicotine replacement as a means of curbing cravings. Launched in the US in 1998, GSK's Zyban® (sustained-release bupropion) was the first nicotine-free prescription tablet to aid smoking cessation. The next did not come along until August 2006 when **Pfizer** launched its smoking cessation product Chantix™ (varenicline) in the US. Chantix binds to neuronal nicotine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine, thereby helping with withdrawal symptoms. The drug also prevents nicotine binding to these receptors,

so reducing the effect of nicotine if patients resume smoking. In clinical trials, Chantix helped 44% of smokers quit by the end of 12 weeks of therapy, compared with 30% of those who received Zyban®, and 17% of those who received a placebo. The study also showed that patients on Chantix had a reduced urge to smoke. Evaluate Pharma predicts that Chantix will have worldwide sales of US\$1 162 M in 2012 – more than the sales of any nicotine replacement product.

The approval of Chantix was a positive event for developers of nicotine vaccines, as it provided a validation of their mechanism of action, for both Chantix and the vaccines work by blocking nicotine from reaching receptors inside the brain and thus eliminating the pleasurable and addictive response to smoking. Furthermore, an effective vaccine could offer additional and significant advantages over Chantix in areas such as duration of response and prevention of relapse. Once a tablet such as Chantix is stopped, patients will still be susceptible to the addictive effects of smoking; in contrast, the antibodies produced following vaccination are expected to last up to 12 months or more. Booster doses of the vaccine may also extend the protective antibody response for periods beyond a year.

CYT002-NicQb faces direct competition from two other nicotine vaccines: **Celtic Pharma's** TA-NIC, which is expected to start Phase II trials in the latter half of 2007, and **Nabi Biopharmaceuticals'** NicVAX®, which has just shown proof-of-concept in Phase IIb.

TA-NIC originated with **ImmuLogic Pharmaceutical** but, in early 1999, ImmuLogic sold its vaccine programmes for the treatment of nicotine and cocaine addiction to **Cantab Pharmaceuticals** (Deal no. 03538). Under the terms of this agreement, Cantab was to pay US\$9 M via the issue of up to 2,566,845 new Cantab ordinary shares of 2p, each in the form of ADSs, in return for two vaccine programmes and US\$6 M in cash to help fund the development of these vaccines. Cantab was also to pay ImmuLogic a maximum of US\$11 M in milestone payments contingent upon successful development of the two programmes to the end of Phase II trials, as well as royalties on worldwide sales. Subsequently, in 2001, Cantab was acquired by **Xenova** (Deal no. 07580), and in January 2003, Xenova bought out all remaining ImmuLogic rights to future milestone and royalty payments relating to TA-NIC and another of Xenova's development-stage vaccine programmes, TA-CD, for US\$1 M (Deal no. 03538). Xenova was acquired by Celtic Pharma Development UK in September 2005, and is now operating as a wholly owned subsidiary of Celtic (Deal no. 20830). TA-NIC is not as far along in development as CYT002-NicQb and NicVAX: it is expected to enter a Phase II study in the US in 2007, and to be filed for registration with the US FDA in 2009.

Like Cytos, Nabi developed its nicotine vaccine internally, obtaining significant funding for NicVAX from external sources. In September 2005, the company received a US\$4.1 M grant from the **US National Institute on Drug Abuse** (NIDA), of the **NIH**, and this is expected

to fully offset the external costs of the Phase IIb proof-of-concept clinical study (Deal no. 21637). NIDA has also contributed significant scientific and clinical expertise to the programme, and has funded the costs for toxicology testing and earlier clinical trials in the US. Nabi expects to continue to secure outside funding to support the cost of Phase III efficacy studies. The company has also stated that it intends to seek a commercialisation partner for NicVAX, preferably one with an existing sales base targeting primary care physicians. Within future partnering relationships, there may also be opportunities for Nabi to market NicVAX within the hospital setting, which would take advantage of the company's existing commercial strength. CYT002-NicQb and NicVAX are at about the same stage of development, but it is currently unclear which has the most potential.

Impact on Novartis

The Novartis–Cytos deal reflects the trend for a growing number of biotech product acquisitions by major pharmaceutical companies. Novartis has recently made a number of licensing deals (Table 1), most noticeably its April 2007 US\$890 M agreement with **Antisoma** for rights to the Phase II lung cancer drug ASI404 (Deal no. 27035).

Novartis has made vaccines a key part of its growth platform following its 2006 acquisition of US vaccines company, **Chiron**, for US\$5.1 B (Deal no. 22116). The company will therefore be able to use its strong in-house vaccine expertise to develop and market CYT002-NicQb. Novartis has said that it plans to start Phase III trials for the product in 2008. The goal is to achieve antibody levels sufficiently high to be effective in a majority of vaccinated individuals, as well as an optimised treatment regimen for the vaccine.

The stated reason for Novartis acquiring the rights to CYT002-NicQb is to strengthen its respiratory disease portfolio, which includes products in development for cystic fibrosis, RSV, asthma and the smoking-related chronic obstructive pulmonary disease (COPD). The company also markets the Foradil® Aerolizer (formoterol fumarate inhalation powder) for asthma and COPD, and Xolair™ (omalizumab injection) for asthma. Thomas Ebeling, CEO of Novartis, has said that CYT002-NicQb 'complements [the company's] efforts to provide a range of new treatment options to patients and physicians across a wide range of respiratory diseases'. However, the deal involved a relatively small upfront payment, indicating that Novartis may not see the acquisition as a major addition to its product portfolio. This may be due to the fact that smoking cessation products do not typically reach blockbuster status. In addition, many smokers may be unwilling to take a vaccine, as opposed to OTC nicotine replacement therapies. We will have to wait and see how the smoking cessation market greets a nicotine addiction vaccine, and who will win the race between Novartis, Nabi and Celtic to be the first to bring a successful product to the market.

Date (Deal no.)	Licensor	Licensee	Product	Phase of development	Indication	Product type	Financial data
Mar 2007 (26783)	Novartis Pharma	TopoTarget	Zemab® (recombinant antibody toxin)	Phase I	Breast cancer, other cancers	Antibody	-
Mar 2007 (26849)	Bayer Schering Pharma	Novartis	Betaseron® (interferon beta-1b)	Launched	Multiple sclerosis	Protein	-
Apr 2007 (27035)	Antisoma	Novartis	ASI404 (DMXAA)	Phase II	Lung, prostate and ovarian cancers	Small molecule	Total US\$890 M Upfront US\$75 M
Apr 2007 (27050)	Novartis Pharma	Synosia Therapeutics	rufinamide	Undisclosed	Anxiety and bipolar mood disorders	Small molecule	-
Apr 2007 (27078)	Cytos Biotechnology	Novartis	CYT002-NicQb	Phase II	Nicotine addiction	Vaccine	Total US\$497 M Upfront US\$29 M

Table 1 – Novartis' recent product licensing deals (Source: PharmaDeals® Agreements).

Academia's Cash Cow: Royalty Streams

Partnering with industry is the only approach for academic and research institutions to progress their promising drug candidates to market. The most savvy of these institutions ensure that they extract the maximum value from their innovations by negotiating a good royalty stream. However, because of the high failure rates of preclinical candidates on the journey to market, many of these royalty streams never materialise. For the lucky few whose research results in a marketable product, the resultant cash inflow is a valuable asset.

Institutions have several options when it comes to milking their royalty streams to the maximum. One is simply to take in the cash from their royalties and use that in whatever way they see fit. Of course, the size of the royalties is highly dependent on the state of the market at the time the product goes on sale, and the magnitude of the royalty stream may vary from year to year, depending on the marketing capabilities of their industrial partner, competition and other factors outside the control of the academic institutions. Another option, and one which is occurring more regularly, is to sell the royalty stream to a third party.¹

In 2000, **Yale University** became one of the first universities to do this, when it closed an agreement with **Royalty Pharma** for the sale of the royalty stream from **Zerit**[®] (stavudine) for US\$125 M (Deal no. 27325). The anti-HIV effect of stavudine had been discovered by Yale's scientists in the 1980s. The University had licensed the IP for the technology used to develop Zerit to **Bristol-Myers Squibb** (BMS) in 1988, and had retained some royalties from the sale of the product. These royalties had provided a valuable income for Yale, netting it approximately US\$30 M a year. Nevertheless, the University took the opportunity to sell the royalty stream to Royalty Pharma, thereby securing itself a substantial lump sum, as well as the guarantee of future revenue from a trust created by Royalty Pharma for the purchase of the royalty stream. Selling the royalty stream at its peak of sales (in 2000 these were US\$359 M) was a good move by Yale, and Royalty Pharma received a product with good sales: Zerit, a nucleoside reverse transcriptase inhibitor (NRTI), is administered as one of the main components of anti-HIV cocktails, which, typically, consist of three drugs, two of which are NRTIs.

Understandably, this type of deal is attractive to research institutions, because the future of royalty streams in highly competitive markets can be quite uncertain and institutions are not traditional risk takers. Selling a royalty stream removes the risk associated with the potential of the cash flow and, perhaps more importantly, provides a more immediate source of cash. This can then be invested in different ways, such as the funding of other research projects and technologies, and assistance in the development of an institution's infrastructure and facilities. Yale University used US\$60 M of its payment to help fund the construction of a new classroom and research complex, the **Anlyan Center for Medical Research and Education of Yale University School of Medicine**.

Some institutions have opted towards a more fail-safe tactic, which is the selling of only a part of the royalty stream. In this way, as well as gaining immediate access to cash, the potential of a good revenue stream is retained. This is exactly what the **Sloan Memorial Sloan-Kettering Cancer Center** (MSKCC) did in 2004, when it sold a portion of its US royalty stream for **Neupogen**[®] (filgrastim) and

Neulasta[®] (pegfilgrastim) to Royalty Pharma (Deal no. 15321). This deal was beneficial to MSKCC in two ways: not only did it receive a cash upfront payment of US\$263 M while still keeping a share of the royalties, it also secured equity in Royalty Pharma, at a value equivalent to US\$7 M. The lucrativeness of this deal can perhaps be explained by the nature of the actual drugs involved. Both **Neupogen** and **Neulasta** (which are different formulations of granulocyte colony stimulating factor) are blockbuster drugs indicated for the treatment of chemoprotection/neutropenia, and had annual sales in 2006 of US\$1.2 B and US\$2.7 B respectively. Interestingly, in 1998, **Amgen** (which developed the drugs based on technology developed in collaboration with MSKCC) itself exchanged a royalty interest in **Neupogen** for an equity investment in the company by **Drug Royalty** (Deal no. 02853).

In July 2005, **Emory University**, of Atlanta, Georgia, earned US\$525 M for the sale of its royalty stream for **Emtriva**[®] (emtricitabine) by selling its royalty stream to two companies (Deal no. 21102). The companies concerned, **Gilead Sciences** and **Royalty Pharma**, contributed 65% and 35%, respectively, towards the payment. Here, having two parties share the cost of the purchase cuts the risk involved. Emtricitabine is another anti-HIV drug which is used in combination with other antiretroviral agents, and one of the components of **Truvada**[®] (the other is tenofovir), the sixth largest selling HIV drug in 2006, when it had sales of over US\$1.2 B.

At the time, Emory's payment was the largest lump sum that an academic institution had received for drug royalties. This was until May 2007, when **New York University** (NYU) sold a portion of its worldwide royalty stream for **Remicade**[®] (infliximab) to Royalty Pharma for US\$650 M in cash (Deal no. 27153). Remicade, an anti-inflammatory drug used in the treatment of several conditions, including rheumatoid arthritis, Crohn's disease, ankylosing spondylitis and psoriatic arthritis, had sales in excess of US\$3.7 B in 2006 and was the biggest income generator for NYU, having brought in a total of US\$360 M to the University.

This deal was followed shortly by an announcement of another royalty stream sale, this time between **Massachusetts General Hospital** (MGH) and **Drug Royalty Corporation** (Deal no. 27193). The drug involved was **Enbrel**[®], a blockbuster rheumatoid arthritis drug. Drug royalty paid MGH US\$300 M for the rights to royalties outside of North America. MGH will therefore continue to receive a royalty stream from Enbrel sales, which, in 2006, were US\$2.7 B in the US alone. MGH may have decided to sell its profitable royalty stream because Enbrel faces stiff competition from other drugs, including **Abbott's Humira**[®], as well as Remicade. For MGH a large lump sum may be a more appealing option than having to deal with the uncertainty of a possible decrease in royalties.

Commercialisation of academic research has come a long way since the Bayh-Dole Act of 1980, which gave institutions, rather than the US Government, the IP rights for their own inventions. The benefits that can be reaped from royalty ownership, which are demonstrated by these major deals, will no doubt encourage more institutions to focus on developing innovative new products that have the potential of exerting a substantial impact on the market.

¹PharmaDeals Review 71, May 2006, pages 12–13.

How Companies Source their Licensing Opportunities

Part I: The Need to Partner Continues to Grow

The 2007 BIO International Convention, held in Boston in May, was attended by a record 22,366 attendees, thus demonstrating the ever-increasing popularity of such meetings and reflecting the continued growth and importance of the biotechnology industry. While many attendees will have been enthused by the keynote addresses from inspirational personalities, such as Michael J Fox, founder of **The Michael J. Fox Foundation for Parkinson's Research**, the meeting's *raison d'être* is to talk business. More specifically, a large proportion of attendees will have been in attendance with the primary objective of finding new business partners with whom to develop new drugs: at BIO in 2007 there were in excess of 12,000 one-to-one partnering meetings.

Collaboration continues to drive the development of innovative drugs. Currently around 18% pharmaceutical sales are attributed to in-licensed drugs,¹ and this proportion is only predicted to increase: strong proof, if any is required, that the 'not developed here' attitude is well and truly redundant within the healthcare industry. Yet, as the importance of partnering continues to increase, the process by which potential partners are found continues to challenge industry executives. Those at smaller biotechnology companies will be familiar with the process of finding the most suitable partners for their key drugs, convincing them that their innovation is worthy of partnering, and then negotiating the most favourable deal terms possible. Meanwhile, those at larger pharmaceutical companies must assess large numbers of potential in-licensing targets in order to find those that meet their current strategic requirements.

These two groups of industry professionals face opposing challenges to ensure that this process is as efficient as possible. Biotech companies are competing with hundreds, if not thousands, of other companies, all of whom want to present their licensing opportunities to relatively few potential partner companies. While certain drug development programmes have a sufficiently high profile to ensure that they receive licensing proposals, these are, overall, in the minority, so biotechs must use all available means to introduce their licensing opportunities to prospective partners. Large pharma companies are presented with hundreds or thousands of products and technologies, and must efficiently identify those that can bolster weaknesses in their pipelines.

To examine the challenges that exist in the partnering process, PharmaVentures, in 2006, conducted a survey of licensing executives, asking them how they sourced their licensing opportunities. In total, 236 executives completed the survey. Of these respondents, 43% belonged to 'start-up/emerging' companies,² 39% to 'established/mid-sized' companies,³ and 15% to 'global'-sized companies.⁴ Just over half of the respondents were based in Europe, with a further third from North America. Analysis of the data was split such that results from start-up/emerging, established/mid-sized and global companies could be compared.

¹ Source: Evaluate Pharma®.
² New or emerging companies with no record of sustained profitability.
³ Companies with a history of profitability who generally operate on a limited territorial basis.
⁴ Multinational companies with a true global presence.

Organisation and Resource Management

The importance of licensing has grown so much that it is now arguably the main activity within business development departments in companies of all sizes. To examine how companies have adapted their organisations to this activity, respondents were first asked who currently sources their licensing opportunities (*Figure 1*). Start-up companies were those that were least likely to have a dedicated business development or licensing department, with the shortfall in this resource being taken up by senior or C-level executives, who performed this role in 39% of companies. These companies were also the most likely to use external consultancies to help them source licensing opportunities. Clearly, larger companies have more available capacity for this sort of activity, with nearly three-quarters of established and global companies using dedicated business development or licensing departments to source their licensing opportunities.

The different organisational resource that companies of different sizes have that is dedicated to the sourcing of licensing opportunities is reflected in the amount of time that these companies are required to commit to this task. Start-up companies, as the source of much of the industry's innovation, spend the least proportion of their time having to source licensing opportunities, with 75% of respondents spending 25% or less of their time engaged in this activity (*Figure 2*). There were no respondents in start-up companies that spent close to 100% of their time sourcing licensing opportunities, while at global companies 13% of respondents were solely dedicated to this activity. This result contrasts the smaller companies, which have less need for dedicated personnel continuously sourcing licensing opportunities,

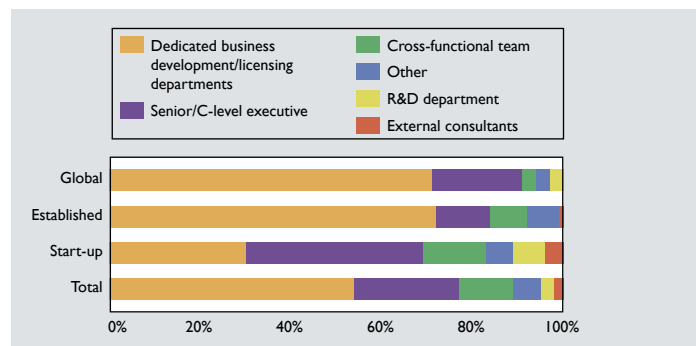


Figure 1 – Who sources your licensing opportunities?

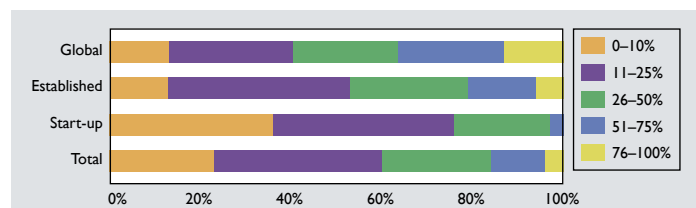


Figure 2 – What proportion of your working time do you spend sourcing licensing opportunities?

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Innovation Sources

Many of today's top-selling drugs represent a trail of innovation and partnering that begins with IP that originated in academic institutions, and is then developed by biotech companies and goes on to be commercialised by global pharma. Survey respondents were asked which types of organisations they had licensed products from in the past 5 years. For start-up companies, academic institutes were the most commonly cited source of licensing opportunities, followed by fellow start-up biotechs (Figure 4). Perhaps, surprisingly, academic institutions were also the most commonly cited source of licensing opportunities for global companies, with 66% of such companies having licensed from academic institutes over the past 5 years, compared with just over 50% of start-up companies (Figure 5). After academic institutes, start-up biotechs and mid-sized pharma and biotechs were each used by 53% of global companies over the past 5 years. Licensing activity does not occur only between companies of different sizes: over one-third of global companies have licensed from other global companies in the past 5 years. For mid-sized companies, the primary source of licensing opportunities over the last 5 years has been both start-up biotechs and mid-sized pharma (Figure 6).

Over 20% of respondents from both start-up and mid-sized companies reported having signed no licensing deals over the past 5 years (Figure 7). This result indicates that a significant proportion of these companies still have enough in their pipeline relative to expectations for companies of their size. In contrast, global companies continue to need to supplement their pipelines, with only one respondent from a global company reporting as having not signed any licensing deals over the past 5 years. Furthermore, global companies also made up the largest proportion of respondents who reported signing between 11 and 25 deals over the last 5 years, and 10% of global companies had signed over 50 deals. Within both start-up and mid-sized companies, the largest proportion of respondents reported signing two to five deals over the past 5 years. Large-scale in-licensing is clearly not an issue for start-up companies, with no respondents reporting as having entered into more than 25 licensing agreements.

A Desire to Optimise

When considering licensing in the pharmaceutical and biotechnology industries, it is usually assumed that it is the greater spending power of global pharma that gives them the biggest advantage over their smaller rivals. However, it is possible that a second important advantage is their dedicated organisational resource, which gives them more efficient sourcing capabilities. What is clear from the data reported here is that, despite the development of the licensing function of company business development departments, there remains a strong desire to optimise the process of sourcing licensing opportunities. In the second part of this feature, presented in next month's *PharmaDeals Review*, we look at how companies source their licensing opportunities and where they source these licensing opportunities from, and ask what part of the opportunity sourcing process these companies wish they could optimise the most.

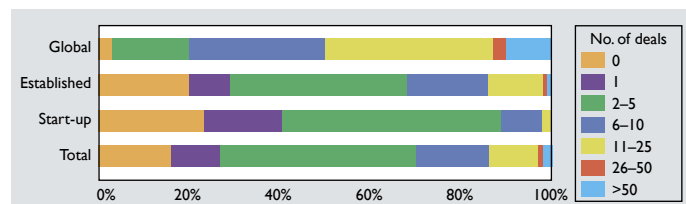


Figure 7 – Number of deals signed last in the last 5 years.

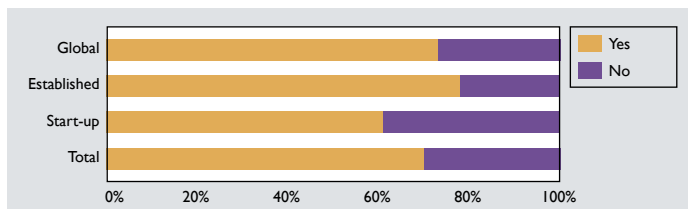


Figure 3 – Do you wish you could optimise the time spent sourcing licensing opportunities?

with the largest companies, which are continually looking for the best innovation to complement their internal R&D and supplement their development pipelines.

To determine whether these differences in capabilities between different sized companies translated into improved efficiency, respondents were asked whether they wished they could optimise the time they spent sourcing licensing opportunities. Interestingly, it was the mid-sized companies that expressed the greatest desire to optimise this process (Figure 3). These results showed that the smallest companies, with the least need to dedicate time to in-licensing, are the happiest with the time spent on this process. This may be because start-up companies have established relationships with local academic institutes from which they may have originated, thus requiring less overall time resource. However, mid-sized companies, which still need to actively in-license, perhaps to a similar degree to big pharma, lack the dedicated resource that is available to global companies, hence putting them at a disadvantage when sourcing licensing opportunities, and making them less efficient in this process.

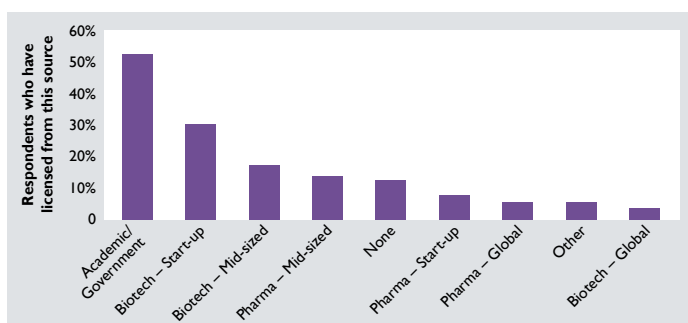


Figure 4 – Licensing opportunity sources for start-up companies over last 5 years.



Figure 5 – Licensing opportunity sources for global companies over last 5 years.

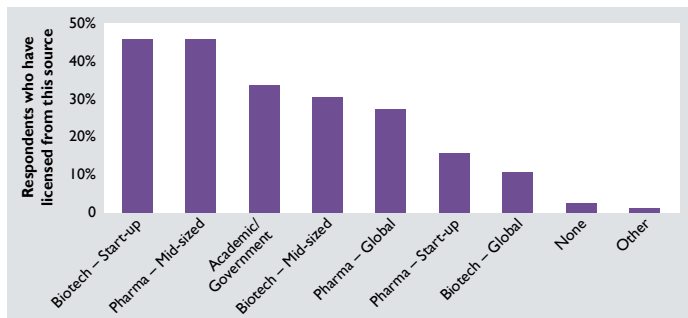
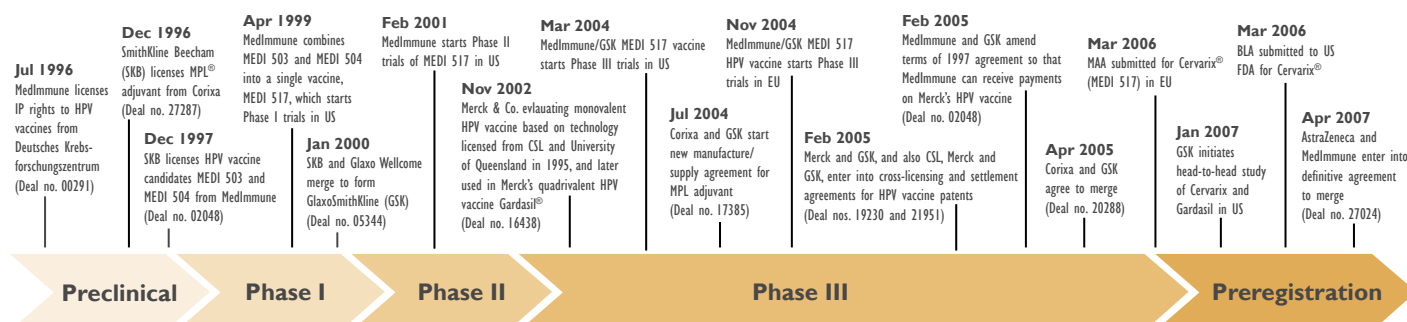


Figure 6 – Licensing opportunity sources for mid-sized companies over last 5 years.

GlaxoSmithKline's and MedImmune's Cervarix® (MEDI 503/MEDI 504, MEDI 517, 580299)



MedImmune and GlaxoSmithKline (GSK) are developing a recombinant, bivalent virus-like particle (VLP) HPV vaccine, Cervarix®, for the prevention of cervical cancer, which is formulated with a proprietary GSK adjuvant system, AS04. AS04 includes another proprietary adjuvant, MPL® (monophosphoryl lipid A), which SmithKline Beecham (SKB) licensed from Corixa in three agreements in the 1990s; the third of these, in December 1996, specifically and exclusively included HPV vaccines. MedImmune licensed the original IP rights to HPV vaccines from Deutsches Krebsforschungszentrum (the German Cancer Research Center) in July 1996. The Cervarix HPV vaccine itself combines two VLPs, MEDI 503 and MEDI 504, which SKB licensed from MedImmune in December 1997; these target HPV 16 and HPV 18, respectively, which are the two most common causes of cervical cancer. Under the terms of the licensing agreement, MedImmune was to be responsible for Phase I and II trials, and manufacture clinical material, while SKB was to be responsible for the final development and marketing of the product.

MEDI 503 and MEDI 504, which are both L1 capsid HPV proteins, completed Phase I trials as separate vaccines in the US, but MedImmune subsequently combined them into a single vaccine, MEDI 517, which entered Phase I trials in the US in April 1999. SKB

and Glaxo Wellcome merged to form GSK in January 2000, and the vaccine entered Phase II trials in the US in February 2001. Meanwhile, in November 2002, Merck & Co. was evaluating a monovalent HPV vaccine based on VLP technology licensed from CSL and the University of Queensland in 1995, which was subsequently used in its quadrivalent HPV vaccine Gardasil®. In 2004, the MedImmune/GSK vaccine entered Phase III trials, both in the US (March) and in the EU (November). Also in that year, Corixa and GSK entered into a new manufacturing and supply agreement for the MPL adjuvant.

In February 2005, Merck and GSK, and also Merck, CSL and GSK, agreed cross-licensing and settlement agreements for the patents used in the HPV vaccines being developed by GSK and Merck, and, in relation to these, MedImmune and GSK amended the terms of the 1997 SKB/MedImmune HPV vaccine alliance. Then, in April 2005, Corixa and GSK agreed to merge. In March 2006, a MAA was submitted for MEDI 517, as Cervarix, in the EU. In January 2007, GSK initiated a head-to-head study of Cervarix and Gardasil in the US and, in the following March, submitted a BLA for Cervarix to the US FDA. There were good reports on 17 April 2007 of Cervarix's effectiveness in also protecting against precancerous cervical lesions caused by HPV viruses other than HPV 16 and 18. Only 6 days later, the proposed merger between MedImmune and AstraZeneca was announced.

Licensing Opportunities

The table below lists some new drug delivery licensing opportunities that are featured in PharmaDeals® Opportunities. If you would like full access to PharmaDeals Opportunities, contact Louise Parker (sales@pharmaventures.com), or if you wish to enter your own business opportunities into the database, please contact Richard Hinde (enquiries@pharmaventures.com).

Identification code	Indication (Phase of development)	Description
LO-0507-10	Alzheimer's dementia co-morbid with depression and/or Parkinson's disease (Phase II)	A novel cholinesterase and brain-selective monoamine oxidase (MAO) inhibitor for the treatment of Alzheimer's disease dementia co-morbid with depression and/or Parkinson's disease is available for licensing. The drug is designed to provide a combination of the improved cognitive function that is given by inhibitors of both acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), the antidepressant activity provided by MAO-A inhibitors, and the neuroprotection against oxidative stress offered by MAO-B inhibitors.
LO-0507-06	Inflammation (Preclinical)	Co-development partnerships are available with pharmaceutical and biotechnology companies that are interested in using a micro-dose formulation of dexamethasone phosphate for the treatment of inflammation. In a preclinical model the extended-release drug has effectively targeted inflamed sites for several weeks following systemic administration. The delivery of micro-doses of the glucocorticoid directly to the area of inflammation reduces the side-effects experienced with other drugs. In contrast to free glucocorticoids, this formulation can have equivalent efficacy at very low doses in treating inflammation, is also less likely to affect non-inflamed tissues and has a much longer duration of effect.
LO-0507-03	Cancer (Discovery)	The licensors have generated a series of peptides that have shown potential <i>in vitro</i> and <i>in vivo</i> as antitumour agents. These act by disrupting the formation of the HOX-PBX cytoplasmic heterodimer and, therefore, prevent this transcription factor from influencing the transcription of the HOX genes. Increased expression of the HOX genes has been seen in many different cancers, so this represents a good therapeutic target. The ability of an optimised peptide to interrupt formation of the HOX-PBX-DNA complex <i>in vitro</i> has been verified, and it has been demonstrated that treatment of multiple cancer cell lines with the peptide induces apoptosis.
LO-0507-01	Drug delivery technology (Discovery)	The licensor has developed a novel proprietary nanoemulsion (droplets 10–50 nm in size) for intranasal, transmucosal, topical, intradermal and transdermal drug delivery of potent peptide, protein and large molecule drugs that are currently only deliverable by injection. The technology is based on a novel, proprietary, versatile, biocompatible, isotropic and thermodynamically stable drug delivery system made from pharmaceutical-grade ingredients, in an alcohol-free system, without chemical enhancers or irritating constituents.

Therapy Focus: Anaemia in Chronic Kidney Disease and Cancer

Anaemia is the most common blood disorder and is caused by a lack of erythrocytes, or a reduced amount of haemoglobin in these cells, both of which result in a degree of oxygen starvation in the body (hypoxia). This leaves sufferers with fatigue, dyspnoea (shortness of breath), palpitations and dizziness.

Haemoglobin needs iron for its construction, and iron-deficiency anaemia is the most common type of anaemia; this type of anaemia is simply caused by low levels of dietary iron, and is treated with iron supplements. Anaemia can also be caused by a lack of vitamin B12 or folic acid in the diet. These vitamins are needed for DNA synthesis and rapid cell production, particularly in haematopoiesis. Other causes of anaemia include heavy periods, internal bleeding caused by, among other factors, ulcers, polyps or tumours, and the destruction of red blood cells by parasites in leukaemia.

Anaemia is most common in menstruating and pregnant women, to the extent that in the US, 20% of all women of childbearing age have iron-deficiency anaemia, compared with only 2% of adult men. One significant area within the anaemia market, and the main focus of this article, is that of the treatment of patients with chronic renal failure (CRF) and with cancer. Anaemia is seen in more than 80% of patients with CRF, and in up to 60% of cancer sufferers, as they do not produce adequate amounts of the haematopoietic glycoprotein erythropoietin.

Erythropoietin

Erythropoietin (EPO) is secreted by the kidneys and is responsible for stimulating the production of red blood cells. In cases where patients cannot produce the protein, they are given an exogenous recombinant form of human EPO (rHu-epo) called epoetin. Previously, transfusions were given to raise the red blood cell count, but the limited supply of blood, risk of infection and expense of this option have driven the demand for treatment with epoetin.

There are four types of epoetin: epoetin alpha, beta, delta and omega, all of which have the same pharmacological actions as endogenous EPO, and all of which, like EPO, are glycoproteins with 165 amino acids. Epoetin alpha, beta and omega are all products of genetically engineered hamster cells, but while epoetin alpha and beta are produced by Chinese Hamster Ovary (CHO) cells, epoetin omega is produced by Baby Hamster Kidney (BHK) cells; these three epoetins have the same sequence of 165 amino acids, but differ in their glycosylation patterns. Epoetin delta is the only epoetin to be produced in human cells, so its glycosylation profile is human, which means that it may be less immunogenic than the hamster-derived epoetins. All of the epoetins act as a treatment for anaemia rather than a cure for the underlying cause, so unless the cause is corrected, treatment with these products must be continued indefinitely.

Current Treatments

Epoetin alpha was first developed in 1984 by a 50:50 joint venture between **Amgen** and **Kirin (Kirin-Amgen)** and, in 1989, became the first marketed epoetin. As Amgen carried out most of the initial

work on epoetins, the company gained many of the patents covering epoetin technology. Amgen's European patents expired in 2004 but its US patents will not expire until 2013–15. In order to protect its market, Amgen has been involved in several legal disputes, which will be highlighted later.

The Kirin-Amgen joint venture granted marketing rights to Amgen for the sale of epoetin alpha in the US for patients with CRF on dialysis. and, in the US, Amgen markets epoetin alpha as **Epogen®**. **Johnson & Johnson (J&J)** also markets epoetin alpha in the US for all indications outside Amgen's remit, following a licensing agreement between the companies dating back to 1985. These rights were gained through **Ortho Pharmaceuticals** (of J&J), and have been passed to **Ortho Biotech Products** (of J&J), which markets the drug under the name of **Procrit®**. Through **Janssen-Cilag**, J&J also has the rights to epoetin alpha in all indications outside the US, China and Japan. Janssen-Cilag markets epoetin alpha as **Eprex®** in New Zealand, the UK, France, Argentina and Brazil for the treatment of anaemia in CRF patients and in patents with non-myeloid malignancies. Within Argentina, a second company, **Immuno**, also markets epoetin alpha as **Epoimmun®** for anaemia associated with chemotherapy in non-myeloid cancers and in zidovudine-treated HIV patients. The co-discoverer of epoetin alpha, Kirin, markets the drug as **Espo®** in China and Japan. Worldwide, **Procrit®/Eprex®** and **Epogen®** were ranked as the 13th and 27th biggest selling drugs in 2006 with sales of US\$3.18 B and US\$2.51 B, respectively.

Since the initial epoetin alpha (a first-generation EPO), Kirin-Amgen has also developed a second-generation hyperglycosylated EPO called darbepoetin alpha (**Aranesp®**). This EPO analogue has two different amino acids which permit a higher degree of glycosylation. In comparison with the other epoetins, which have a half-life of approximately 8 hours, darbepoetin alpha has a serum half-life of 48 hours, and also has a higher relative potency, which further increases with extension of the administration interval. This reduces the number of injections needed from the existing frequency of one to three times a week – with the first-generation epoetins – to once every 1–2 weeks with darbepoetin. The less frequent administration of **Aranesp®** minimises patient inconvenience, improves compliance and may reduce drug costs in the long term. As a result of these benefits, **Aranesp®** has gained significant market share since its approval in 2001. As can be seen in Figure 1, **Aranesp®** is now the biggest selling epoetin drug and has the 8th highest worldwide sales of all drugs.

At approximately the same time that epoetin alpha was being developed, the **Genetics Institute** (now **Wyeth**) was working on its own epoetin (epoetin beta). In 1984, **Chugai Pharmaceutical** licensed the rights to develop and market epoetin beta in Japan and the US from the Genetics Institute. In the following year, the Genetics Institute also entered into a licensing agreement with **Boehringer Mannheim** (now **Roche**, following Roche's acquisition of the company in 1997; Deal no. 01280), which allowed **Boehringer** to develop and market the product in Europe. Through its merger with **Nippon Roche** in October 2002, Chugai then became Roche's exclusive pharmaceutical representative in Japan (Deal no. 09458).

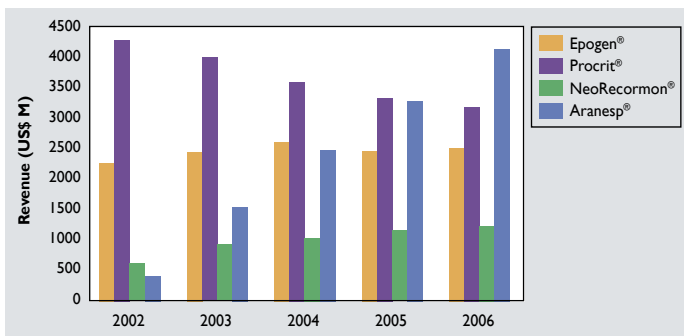


Figure 1 – Worldwide revenue of the top four epoetin drugs in the period 2002 to 2006.

Chugai has marketed epoetin beta (as Epogin®) in Japan since April 1990 for the treatment of anaemia associated with renal failure, and the product has also gained approval for the treatment of anaemia in premature infants. In December 2005, Chugai filed for registration and marketing approval of epoetin beta as a treatment for cancer chemotherapy-induced anaemia in Japan.

As Amgen has done with Aranesp, so has Roche developed a second-generation epoetin that requires less frequent dosing. This drug, the epoetin beta NeoRecormon®, can be stored at room temperature for up to 5 days, and was launched in the EU in 2000. NeoRecormon® was originally developed by Boehringer Mannheim and the Genetics Institute, so Roche now licenses it from Wyeth.

Epoetin delta was first developed in a collaboration between **Transkaryotic Therapies (TKT)** and **Hoechst Marion Roussel** (now **sanofi-aventis**) but, in March 2004, **Aventis** (which was originally formed by the merger of **Hoechst Marion Roussel** and **Rhône-Poulenc Rorer** in 1999; Deal no. 03449) returned its rights outside the US to TKT in return for royalties on sales (Deal no. 16084). The drug gained EU approval in March 2002, but its launch was delayed heavily because of a legal battle with Amgen and Kirin-Amgen, who claimed that it infringed their existing patents. The drug is produced in human cells that are genetically engineered in a different manner to the one used by Amgen, and it was felt that this would circumvent Amgen's patent. **Shire** took up the legal battle following its acquisition of TKT in April 2005 (Deal no. 20174), and after a total of 5 years of litigation, the drug (**Dynepo®**) has only just (in March 2007) been launched in Germany, although it should be available EU wide by the end of the first half of 2007.

Epomax/Hemax (epoetin omega) has been on the market for some time. It was originally developed by **Elanex Pharma Group**, which was acquired by **Baxter** in October 2001 (Deal no. 09044). As a result of Amgen's existing patents and its dominant market position, Baxter currently only markets the product in Eastern Europe, Latin America and South-East Asia.

Pipeline Anaemia Drugs

One of the more promising drugs in the anaemia pipeline is Roche's CERA (continuous erythropoietin receptor activator) which, at 130 hours, has a far longer serum half-life than Aranesp. Phase III trials have shown that once 2- or 4- weekly administrations of CERA maintained Hb levels of patients previously on a more frequent epoetin regimen. Amgen has also tried to prevent CERA reaching the market, stating that it impinges on manufacturing patents. However, Roche maintains that the PEGylation technology used in the drug's manufacture – which Roche licensed from **Nektar Therapeutics** in 2004 (Deal no. 15422) – makes it significantly different. CERA is filed for registration

in the US and is in Phase II development for chemotherapy-induced anaemia. In April 2006, Roche submitted a BLA to the US FDA and a MAA to EMEA for the treatment of anaemia associated with chronic kidney disease. Should this drug circumvent Amgen's US patents, it is likely to reduce Aranesp® sales hugely, and is predicted to reach blockbuster status by 2011.

Following CERA, **Affymax's** novel synthetic PEGylated peptide mimetic of erythropoietin (**Hematide™**) may be one of the next to reach the market, and is expected to be cheaper than the other epoetin treatments. This drug, like CERA, was made using Nektar's Advanced PEGylation Technology to prolong its serum half-life (Deal no. 24840). The protein has a completely different amino acid sequence to EPO/epoetin, and should have no problems with Amgen's patents. The product is stable at room temperature, has a reduced immunogenicity and is easily manufactured. In February 2007, Affymax entered into a global agreement with **Takeda Pharmaceutical** for the development and commercialisation of Hematide (Deal no. 23385). The two companies will collaborate on the development of the mimetic in the US, and Takeda will be responsible for development and commercialisation elsewhere. The product is undergoing Phase II development, and could reach the market by 2010 for the treatment of anaemia resulting from CRF, and by 2011 for anaemia in chemotherapy patients. However, with a serum half-life of only just over 70 hours at best, it is unlikely to gain significant market share.

These new products all have the drawback of being injectable drugs that need to be administered by physicians. **Nautilus Biotech**, however, has an orally available EPO drug called **Eporal™**, which is in preclinical development in the US. Research is also being carried out in South Korea with **Han All Pharmaceutical**, with whom a collaboration and licensing agreement was signed in March 2007 (Deal no. 26690). This protein has small changes in its amino acid sequence, which slow down its breakdown in blood, tissues or intestines.

Moving away from the EPO anaemia treatments, **Biopure** has developed **Hemoglobin glutamer-250 (Hemopure®)**, a stable formulation of ultrapurified, polymerised bovine haemoglobin, for use in transfusions. This has been developed primarily to treat anaemia, but could also be used as a treatment for shock, ischaemia and sickle cell disease. Worldwide, Hemopure is in various stages of clinical development, but it has been launched in South Africa, and is awaiting registration in the US and UK.

The Threat to Amgen and J&J

The market for drugs that boost haematopoiesis in anaemic patients is considerable: the top four drugs earned almost US\$11 B in 2006. The current epoetin drugs have brought companies such as Amgen, Kirin, J&J and Roche a healthy income, but three major threats have jeopardised this position. The first obvious one is the introduction of competing products such as CERA into the anaemia market. The second has already arrived in the form of clinical trial results published at the start of 2007, which highlighted the severe cardiovascular dangers associated with long-term epoetin use. This forced the FDA to issue a black box warning with all epoetin treatments. These safety warnings have been blamed for the 8% fall in Aranesp® sales between the last quarter of 2006 and the first quarter of 2007, but the long-term effects are unclear. The third threat comes from the impending introduction of biogenics – or biosimilars. Specific guidelines from EMEA for biosimilar EPOs were put into effect in July 2006, and the first biosimilar EPO could be launched later in 2007. Biosimilars could capture a large proportion of the anaemia market.

Licensing

ArQule and Kyowa Hakko Kogyo Sign Exclusive Licence Agreement for Cancer Drug in Asia

ArQule, a US-based biotechnology company engaged in the research and development of next-generation, small molecule cancer drugs, has granted Japanese company **Kyowa Hakko Kogyo** an exclusive licence to develop and commercialise ARQ 197 in Japan and parts of Asia (Deal no. 27099). Under the terms of the agreement, ArQule will receive **US\$123 M** in upfront and potential development milestone payments, including a **US\$30 M** cash upfront licensing fee. In addition, the agreement includes undisclosed sales milestone payments and double-digit royalties on net sales of ARQ 197. Kyowa will be responsible for clinical development costs and commercialisation of the compound in Japan, China, Hong Kong, South Korea and Taiwan.

ARQ 197 is the lead product from ArQule's Cancer Survival Protein modulation programme. This small molecule mediates its effects by inhibiting the activity of c-Met, a receptor tyrosine kinase that plays multiple key roles in human cancer, including cancer cell growth, survival, angiogenesis, invasion and metastasis. Preclinical findings have demonstrated that ARQ 197 inhibits c-Met in a wide range of human tumour cell lines, and possesses antitumour activity against several types of xenografted human tumours in mice. Phase I data demonstrated clinical tolerability, pharmacokinetics and signs of antitumour activity in cancer patients with a broad range of metastatic solid tumour types who had failed earlier treatment regimens.

ArQule's portfolio consists of two other clinical stage compounds – ARQ 501 and ARQ 171. These E2F1 pathway activators result from an alliance with **F. Hoffmann-La Roche**, entered into in April 2004 (Deal no. 16176). Under the terms of this agreement, Roche obtained an option to license drugs resulting from ArQule's E2F programme in the field of cancer therapy.

ARQ 197 adds to Kyowa's strong portfolio of anticancer drugs, which include mitomycin, 5-fluorouracil (5-FU), Leunase® (*Escherichia coli* L-asparaginase), Adriacin® (doxorubicin), Hysron® H-200 (medroxyprogesterone acetate), dacarbazine, Farmorubicin® (epirubicin), Platosin® (cisplatin) and Navelbine® (vinorelbine). This oncology franchise positions the company strongly in Asian markets, and will allow it to develop and commercialise ARQ 197 effectively.

Isis Licenses Antisense Programme to BMS for Cardiovascular Collaboration

Bristol-Myers Squibb (BMS) and **Isis Pharmaceuticals** have entered into a collaboration to discover, develop and commercialise novel, antisense drugs targeting proprotein convertase subtilisin kexin 9 (PCSK9) for the prevention and treatment of cardiovascular disease (Deal no. 27053). As part of the collaboration, Isis has licensed to BMS exclusive access to its PCSK9 research programme, in exchange for a **US\$15 M** upfront licensing fee, milestone payments that include up to **US\$168 M** for the first drug in the collaboration, and at least **US\$9 M** in research funding over a period of 3 years. BMS will also pay Isis royalties on sales of products resulting from the collaboration.

Antisense technology prevents the production of proteins involved in disease processes by interrupting the translation phase. PCSK9 contributes to high levels of LDL cholesterol and, with its second-generation antisense PCSK9 compounds, Isis has shown, in mice, that reducing PCSK9 leads to increased levels of LDL receptor and, consequently, to lower LDL-cholesterol in the bloodstream. Decreasing LDL-cholesterol is thought to play a key role in reducing the risk of coronary artery disease.

Isis has a number of products in development, but only one antisense-based drug has yet reached commercialisation – Vitravene® (fomivirsen), which is approved for cytomegalovirus (CMV) retinitis accompanying HIV infection. Vitravene was developed during a collaborative research programme between **Eisai** and Isis, a revision of which, in August 1996, granted Isis full control of both development and commercialisation activities (Deal no. 00391). In July 1997, **CIBA Vision** (now **Novartis Ophthalmics**) acquired exclusive worldwide distribution rights for Vitravene (Deal no. 01455), and the product was launched in the US in 1998 – the first antisense compound to receive marketing approval in that country.

The agreement with BMS is the third in 2007 in which Isis has granted licences to its antisense drugs. In the first, **Atlantic Healthcare**, a private UK group based in Cambridge, acquired from Isis the exclusive worldwide rights to the intercellular adhesion molecule-1 (ICAM-1) antisense compound alicaforsen, and its derivatives, for all indications and all formulations (Deal no. 26967). In the second agreement, Isis granted **novosom** an exclusive option to acquire an exclusive, worldwide licence to antisense inhibitors targeting the CD40 membrane protein, for all indications (Deal no. 26977).

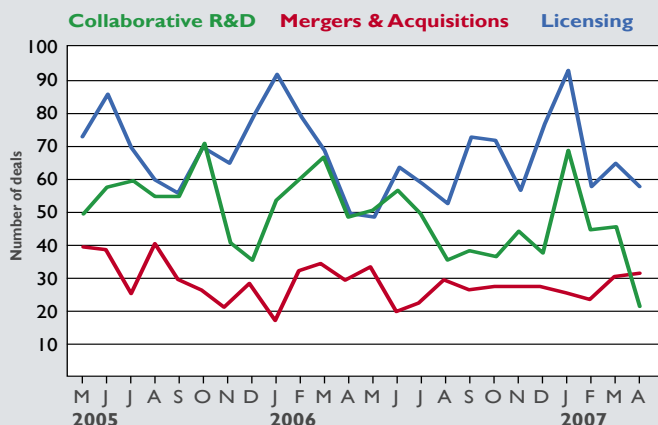
Isis shares opened at US\$10.48 on the day that this third deal with BMS was announced, up 6.3% from close on the previous day.

Research & Development

BMS and Pfizer to Collaborate on Thrombotic and Metabolic Disorders

BMS and **Pfizer** have entered into a worldwide collaboration agreement to develop and commercialise the anticoagulant apixaban, which was discovered by BMS scientists (Deal no. 27087). Apixaban is being studied for the prevention and treatment of a broad range of arterial and venous thrombotic conditions. The total deal is worth **US\$1 B**. This is inclusive of a **US\$250 M** upfront payment which Pfizer will make to BMS, as well as development and regulatory

PV Index Monthly tracking of sector specific deals



milestone payments from Pfizer to BMS, which may add up to **US\$750 M**. In terms of the development costs, Pfizer is the majority contributor, paying for approximately 60% of these expenses, with BMS covering the rest.

Apixaban is a novel, oral, highly selective, factor Xa inhibitor that is currently at different clinical trial phases for various thrombotic conditions. A worldwide study for the prevention of venous thromboembolism and stroke in patients with atrial fibrillation is now undergoing Phase III trials. A Phase II study for the treatment of acute symptomatic deep vein thrombosis (DVT), among other conditions, is also taking place. Compared with current treatments, Apixaban may represent a more targeted approach to these conditions – because it targets one factor – while other treatments tend to target several factors within the same pathway. If approved, apixaban could be the first oral factor Xa inhibitor treatment on the market in over 50 years, although BMS and Pfizer would face competition from other companies who are also developing factor Xa inhibitors.

The large value of this deal can be put down to the size of the market that apixaban is targeting. Cardiovascular diseases are the biggest killers in the developed world, with thrombosis a major factor in this sector. The companies have agreed to share commercialisation expenses, profits and losses equally. So, should apixaban make it to market, they will stand to gain equally from the transaction, which, given the nature of the market, may result in huge profits.

On the same day that the deal for apixaban was announced, BMS and Pfizer announced a second deal, this time for a Pfizer discovery programme that includes several advanced preclinical compounds (Deal no. 27096). The companies have agreed to collaborate on the research, development and commercialisation of these compounds, which have applications for the treatment of metabolic disorders, namely, obesity and diabetes. Pfizer will contribute 60% towards the development costs but, unlike the terms of the first deal, it will have a 60%, rather than a 50%, share of all profits/losses. Though the total value for this deal has not been disclosed, a **US\$50 M** upfront payment will be made to Pfizer by BMS.

Mergers & Acquisitions

Mylan to Acquire Generics Business of Merck KGaA

Canonsburg, Pennsylvania-based **Mylan Laboratories** has made a bold move to secure its future in a generics industry rapidly moving towards fewer, bigger companies, by signing a definitive agreement to acquire 100% of the shares of **Merck KGaA's** generics business in an all-cash consideration of **€4.9 B (US\$6.6 B)** (Deal no. 27219).

The deal represents a good price for Merck as it was at the top end of the expected sale value. Mylan can also be pleased after beating off competition from **Ranbaxy, Actavis** and **Teva Pharmaceutical Industries** to acquire the fourth largest generics business in the world. While Merck's generics business only had a book value of US\$1.3 B, this part of the company's business had 2006 sales of US\$2.4 B (almost double Mylan's sales), being surpassed only by those of Teva, **Novartis' Sandoz** and **Barr Pharmaceutical**.

By paying US\$6.6 B, Mylan has paid 2.75 times more than Merck's 2006 sales, and more than its own market value. However, when comparing the acquisition price with the earnings ratio for similar generics deals, Mylan does not seem to have paid over the odds.

STADA Arzneimittel's acquisition of Serbian **Hemofarm** (Deal no. 27347), **Barr Laboratories' acquisition** of Croatian **PLIVA** (Deal no. 24597), and **Zentiva's** acquisition of Turkish **Eczacibasi Pharmaceuticals** (Deal no. 26784), all had earnings ratios of only slightly less, at approximately 2.5.

Unfortunately for Mylan's shareholders, to finance the deal, Mylan plans to suspend the dividend on its common stock and to issue US\$1.5–2 B of equity and equity-linked securities that may dilute shareholders' earnings. The deal is expected to reduce full-year earnings per share the first year after the merger, break even in year two, and be accretive thereafter. Mylan has secured fully committed debt financing from **Merrill Lynch, Citigroup** and **Goldman Sachs**.

Merck's generics business represents a good fit for Mylan as Merck's worldwide presence in 90 countries has little overlap with Mylan's existing operations, and complements Mylan's strong US presence. This substantial global footprint will provide an excellent platform for growth, and the size of the company will allow for greater operating efficiencies and increased economies of scale – a feature in high demand in the generics industry. The combined company will offer some 560 products across several therapeutic areas via dosage forms including solid orals, patches, controlled-release and high-potency products, antibiotics, sterile liquids, inhalants and creams, which have a combined revenue of US\$4.2 B.

Merck will use the revenue from the deal to pay off its remaining debt of US\$5.5 B incurred following its US\$13.3 B acquisition of **Serono** in September 2006 (Deal no. 25251). The sale of its generics business now allows Merck to focus its resources on further growth within its pharmaceuticals and chemicals business sectors. The transaction remains subject to regulatory review in relevant jurisdictions, and certain other customary closing conditions, and is expected to close in the second half of 2007.

Sun to Acquire Taro for US\$454 M

On 20 May, India-based **Sun Pharmaceutical Industries** signed a definitive agreement to acquire the Israeli company **Taro Pharmaceutical Industries**, in a deal valued at **US\$454 M** (Deal no. 27296). Taro has traded publicly in the US since 1961, and its equity is valued at **US\$230 M**, or US\$7.75 per share, a premium of 27% compared with the 18 May closing share price of US\$6.10. The deal also includes **US\$224 M** for the refinancing of Taro's debt and, in addition, Sun will provide interim financing of **US\$40.7 M**. This is the second-largest overseas buyout by an Indian pharmaceutical company. The largest so far was the US\$573 M acquisition of **betapharm** by **Dr. Reddy's Laboratories** in February 2006 (Deal no. 23426).

On 19 May, **Franklin Advisors** and **Templeton Asset Management** which, together, hold 9% of Taro's shares, sought a temporary injunction from the Tel Aviv District Court to stop Taro from entering into the deal. The Court determined not to issue the injunction, and the sale will proceed as planned.

Sun and Taro both manufacture branded generics. Sun's international presence has been achieved through internal growth and through acquisitions that were chosen to allow Sun access to new therapy areas or geographical territories. Taro will provide Sun with dermatology and paediatrics expertise, plus approved manufacturing sites in Canada and Israel. Sun has US\$400 M set aside for more acquisitions of US generics companies, and there is speculation of an increase in similar transactions by Indian companies as rivals jostle for competitive positions in the US.

Geymonat SpA

Geymonat SpA, which was founded in 1928, is a privately held Italian company with legal headquarters in Catania, and with laboratories and manufacturing facilities in Anagni, near Rome. The company specialises in the research, production and international distribution of ethical (prescription) medicines (about 20 products), OTC medicines (eight products), food supplements (three products), medical devices (five products) and dermatological cosmetics (or dermocosmetics; four products). Geymonat devotes particular attention to children, women and the elderly, and it has developed a list of products for indications in: paediatrics, gynaecology, angiology, gastroenterology, rheumatology, orthopaedics and vascular pathologies. The products have prestigious trade marks and are internationally known entities.

The company markets its products both in Italy and internationally. It has business relationships with several notable companies, including **Boehringer Ingelheim**, **Cosme de Beaute** (of Japan), **Dompé International**, **Grupo Ferrer International**, **Galenica Group** (headquartered in Switzerland), **GlaxoSmithKline**, **Natural Science** (of Iowa, US), **Nippon Organon** (of Organon (of Akzo Nobel)), **Procter & Gamble**, **Laboratoires Seaderm** (Brussels, Belgium) and **HIPP** (Europe).

Geymonat started building its manufacturing site at Anagni in the 1980s. The site has several departments dedicated to the production of medicinal products, a modern biotechnology research laboratory and a pilot unit for the synthesis of complex organic substances. The production plant is equipped and authorised for the production of various pharmaceutical formulations, including: solid orals; powders in tablets, sachets and capsules; sterile products manufactured under aseptic conditions (solutions and lyophilates in vials, powders in bottles); ointments; suppositories and ovules; and liquids for oral use (solutions, drops and syrups). An advanced system of quality assurance guarantees that any operation carried out at the manufacturing site is in conformity with GMP. The production capacity, and the capability to manufacture various formulations, caters for the requirements of both Italian and foreign markets, as well as specific toll (contract) manufacturing, which ensures reliability and high quality standards.

The technology research laboratory was set up in 1993 at the Anagni manufacturing site for the company's R&D activities. This department is engaged in the study, setting up and optimisation of production processes (on a laboratory scale) related to pharmacologically interesting recombinant proteins, mainly derived from strains of *Escherichia coli*, and mainly in the field of angiogenesis. The whole process is based on the yield and the quality of the final product, and it is also planned to make scale-up easier. In conformity with current EC guidelines on medicinal products obtained by recombinant DNA methods, quality control is developed to define the identity, purity and biological activity of recombinant protein products obtained.

The main field of activity of the technology research laboratory (and its main research project) is the development of production and control processes for placental growth factor-I (PIGF-I), a protein which has many structural and functional analogies with vascular endothelial growth factor-A (VEGF-A). Pharmacotoxicological data obtained from animal models have shown that PIGF-I has high angiogenic activity, low toxicity and a protective effect in myocardial

ischaemia. A variety of therapeutic applications have been identified for PIGF, including ischaemic heart disease and peripheral arterial occlusive disease, as well as bone fracture and wound healing.

Geymonat isolated PIGF-I in co-operation with Dr Maglione and colleagues of the **Istituto Internazionale di Genetica e Biofisica** (IIGB; International Institute of Genetics and Biophysics), now **Istituto di Genetica e Biofisica "Adriano Buzzati-Traverso"** (IGB; Institute of Genetics and Biophysics "Adriano Buzzati-Traverso"), both part of the CNR (**Consiglio Nazionale delle Ricerche**; the Italian National Research Council). This was accomplished via the isolation of cDNA derived from a gene bank preparation of placental mRNA. The technology available at Geymonat can be used to synthesise PIGF-I and exploit it for its angiogenic properties. The company is continuing its research on PIGF-I in co-operation with important universities and pharmaceutical companies, in particular in the area of haemato-oncology. Geymonat has also developed PIGF-I mutein, which might have interesting applications in the field of therapeutics, diagnostics and cosmetics.

Strategic Alliance History

Partner(s)	Type of Alliance	Date (Deal no.)	Product/technology/ interest area
ThromboGenics Ltd, European Union	Funding	Jan 2007 (26277)	Geymonat and ThromboGenics receive funding over 2 years from EU Framework Programme 6, as part of the VASOPLUS consortium, to fund development of PIGF (placental growth factor) and PIGF analogues to treat ischaemic heart disease, peripheral arterial occlusive disease, tissue regeneration and wound healing
ThromboGenics Ltd, Roche Diagnostics	Licensing, Rights	Oct 2006 (27141)	Roche licensed PIGF angiogenic factor from Geymonat and ThromboGenics for diagnostic applications
ThromboGenics Ltd	Collaborative R&D	Mar 2004 (15797)	Development of PIGF angiogenic factor in conditions such as ischaemic heart disease
Istituto Internazionale di Genetica e Biofisica (IIGB; International Institute of Genetics and Biophysics) of the CNR (Consiglio Nazionale delle Ricerche; Italian National Research Council)	Collaborative R&D	Undisclosed	PIGF-I angiogenic factor

Product Development Pipeline

Product	Indication	Status
PIGF-I	Angiogenic factor for ischaemic heart disease and peripheral arterial occlusive disease, as well as bone fracture and wound healing	Undisclosed
PIGF-I mutein	Mutant (or altered) PIGF-I, with possible applications in [angiogenesis-related] therapeutics, diagnostics and cosmetics	Undisclosed

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Conferences | A brief guide to some of the major conferences coming up over the next few months

Date	Conference name	Organiser	Location
Jun 4–5	Pricing & Reimbursement in North America: Achieving Pricing & Reimbursement Success in the USA Market	SMi	London, UK
Jun 4–6	8th Drug Discovery Leaders Summit	Oxford International	Athens, Greece
Jun 6–7	3rd Annual Global Protein Summit	SMi	London, UK
Jun 11–14	bioLOGIC Europe 2007	Terrapinn	Geneva, Switzerland
Jun 12	Strictly Financing	Medicon Valley Academy (UK Medicon Valley Bioscience Alliance)	Copenhagen, Denmark
Jun 12–13	BioDevice Partnering 2007: Building Convergent Technologies	EBD Group	Zurich, Switzerland
Jun 13	Medical Innovation Forum	Enterprise Events	London, UK
Jun 18	13th BioTech & Finance Forum	BioRegio STERN	Stuttgart, Germany
Jun 18–20	BIO VentureForum-East 2007	BIO	Montreal, Canada
Jun 21	EPIC – European Partnering & Investment Conference	Vitesse Media	London, UK
Jun 26–28	14th Annual Euro-Biotech Forum	Windhover Information	Paris, France
Jun 27–28	Pharmaceutical Portfolio & Lifecycle Management Conference	SMi	London, UK
Jun 27–29	ERBI's 9th Annual BioPartnering Exchange Event 2007	ERBI	Cambridge, UK
Jun 28	Pharmaceutical Intellectual Property Conference: Litigation and patent protection for strong asset management	SMi	London, UK
Jul 7–11	34th Annual Meeting & Exposition of the Controlled Release Society	Controlled Release Society	Long Beach, CA, US
Jul 10–11	The Pharma-Bio Outsourcing Conference and Exhibition	DMG World Media	London, UK
Aug 1–2	5th Annual Australian Biotechnology Summit	UNSW Centre for Health Informatics	Sydney, Australia
Sep 4–5	European Biomarkers Summit	Select Biosciences	Amsterdam, Netherlands
Sep 5–6	Drug Discovery Partnerships & Outsourcing: Source earlier research alliances to cut costs, speed time to clinic and fill pipeline needs	IQPC	London, UK
Sep 18–20	BioBusiness Network 2007: The Premier Global Bio-Partnering Event	Worldwide Business Research	Geneva, Switzerland
Sep 19–20	Advanced Valuation of Pharmaceutical Strategic Alliances	PharmaVentures	Vancouver, Canada
	 A 2-day advanced workshop on insights into cutting-edge approaches, methods and techniques for the valuation of pharmaceutical products, technologies, alliances and ventures. The workshop is aimed specifically at more experienced deal makers, financial specialists and other professionals. Visit www.pharmaventures.com		
Sep 24–26	BIO Mid-America VentureForum 2007	BIO	Milwaukee, WI, US
Sep 25–27	Pharmaceutical Strategic Alliances	Windhover Information	New York, NY, US
Sep 26–27	FT Global Pharmaceutical & Biotech Conference	FT Conferences	London, UK
Oct 3–5	BioContact Québec 2007, 14 ^e édition: A Biopharmaceutical Partnership Symposium	BioContact	Quebec, Canada
Oct 7–9	15th Annual BioPartnering Europe	Technology Vision Group	Quebec, Canada
Oct 9–11	BIO InvestorForum 2007	BIO	San Francisco, CA, US
Oct 10–12	BioNetwork 2007: The 6th Annual Pharmaceutical-Biotech Partnering Conference	Worldwide Business Research	Laguna Miguel, CA, US
Oct 14–18	LES 2007 Annual Meeting. The New Deal: Competing in a Global Economy	Licensing Executives Society	Vancouver, Canada
Oct 21–24	AusBiotech National Conference 2007	AusBiotech	Brisbane, Australia
Nov 12–14	BIO-Europe 2007: Building Value Through Partnerships	EBD Group	Hamburg, Germany

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