

# Effective Deal Making in Drug Delivery

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# Introduction

Drug delivery continues to be an increasingly important sector in the pharmaceutical industry and an area in which effective deal making is essential for survival and growth. A great proportion of small companies specialising in drug delivery systems rely upon deals for revenues, and larger pharmaceutical companies need access to their expertise and innovative technologies for the development of new products. A third category comprises drug delivery companies that have transitioned into fully integrated pharmaceutical companies. The market is attractive: the market for drugs using special delivery systems has grown from \$26 B in 2000 to over \$60 B in 2006<sup>1</sup> and now accounts for over one tenth of the total pharmaceutical market.

Effective deal making is particularly important in the present economic climate with western economies experiencing a significant downturn compared to recent years. A marked loss of confidence in equity markets has continued to weaken public share offerings such that they are not currently viewed as an attractive means of raising the money that is required for rapid growth of drug delivery companies. Indeed, following the burst of the technology bubble in 2001 and the subsequent drop of market indices, 2006 and 2007 showed some slow recovery. For example, NASDAQ posted 88% and 92% of the 2001 value in 2006 and 2007, respectively, but has slipped back in the first 6 months of 2008 to 2005 levels. By the second half of 2008, the biotech/pharma IPO window has completely shut down and markets have dropped dramatically. The pharmaceutical and biotech sectors have a tendency to operate in something of a bubble, and whilst not experiencing the dramatic downturns of other sectors, there has nonetheless been significant drops and the drug delivery sector appears to have been hit particularly hard. As a result there has been even more pressure on dealmakers to strike the right deals and strategic alliances to fuel growth. The rapid rise in the number and value of deals recorded in PharmaVentures' PharmaDeals® v2 Agreements Database shows the increasing reliance upon the development of strategic alliances for gaining access to innovation and the funds that are required for product development and corporate expansion.

**Effective Deal Making in Drug Delivery** encompasses issues that are vitally important to successful deal making within the drug delivery sector. The report begins with an assessment of the current and evolving drug delivery market, drug delivery companies and the challenges that are facing the drug delivery sector. The key driving factors that underlie the drug delivery sector are considered, including improving the therapeutic index of drugs, improving patient benefit and compliance, increasing the length of patent protection and product life cycle

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<sup>1</sup> Leading Drug Delivery Companies and Technologies. Business Insights 2008

management. The report also reviews the business strategies that are employed for the commercialisation of drug delivery systems and an in-depth analysis addresses drug delivery alliances and their financial terms.

Integral to this report is a searchable management tool, available via the PharmaDeals® web site, which comprises over 29,000 deals that occurred from May 1996 to the end of the third quarter of 2008. This comprehensive source of drug delivery deals enables the gathering of competitive deal information including financial information. In addition, the database assists in obtaining knowledge of company relationships and partnerships that are vital to most drug delivery companies' strategic business objectives.

The report also examines the drug delivery deal making activity of the top 10 pharmaceutical companies by healthcare sales, to help the reader understand the partnering activities of the largest healthcare companies. The valuation methodologies that can be used when formulating deal terms are also described, including principles and rationale, deal benchmarking and financial spreadsheet modelling.

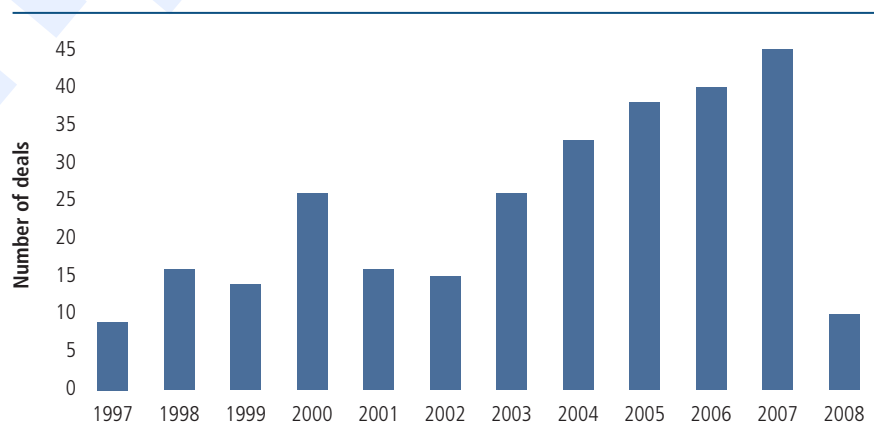
The report includes an account of the process by which drug delivery deals are typically established from the initial steps of identifying the corporate needs, business opportunities and potential partners, through to the establishment of feasibility studies and full commercial alliances. Additionally, examples of genuine drug delivery agreements are provided that cover a variety of deal types including clinical & commercial, marketing, mergers & acquisition and finance deals. These agreements, less the redacted portions, can be accessed via the PharmaDeals® v2 Agreements database.

The drug delivery sector represents a dynamic, rapidly evolving sector as companies vie for partnering positions that will maximise commercial returns. Both market needs and technology innovation continue to drive this special sector, and it will be interesting to witness its evolution over the ensuing years.

launched CDS' Retisert™ ocular implant for uveitis. With its partner, Chiron, CDS previously developed and commercialised Vitrasert® for cytomegalovirus retinitis, also now marketed by Bausch & Lomb. Both Retisert® and Vitrasert® use the AEON™ delivery system. CDS collaboration with Bausch & Lomb dates from July 1999. CDS' pipeline also included Medidur™, an injectable long-term, sustained release product in Phase III trials for the treatment of diabetic macular oedema, which was being developed in collaboration with Alimera Sciences. Other product candidates include CDS PM101 in Phase I development for postoperative pain, and CDS TC 32, which is in preclinical development for coronary restenosis; both these products use the CODRUG™ delivery system. CDS TC 32 is the subject of a collaboration between CDS and Biotronik.

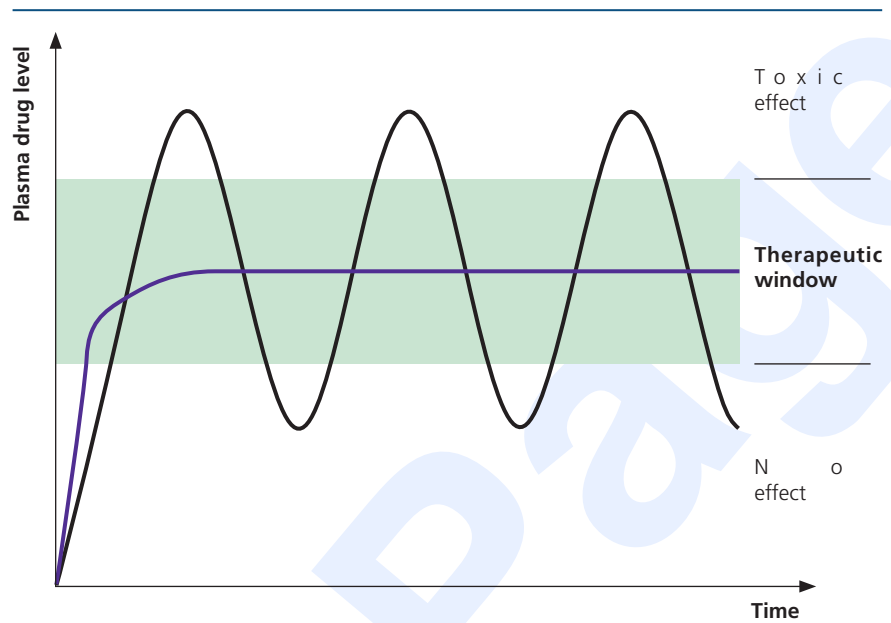
Short- to medium-term, the combined company plans to use pSividas' BioSilicon™ and CDS™ AEON™ drug delivery technologies to develop ophthalmic and anticancer products.

M&A is thus a well-trodden strategy amongst both specialist technology and cross-platform providers in the drug delivery sector. Figure 2 illustrates the level of M&A transactions among companies where at least one party had a focus on drug delivery. The apparently anomalous higher level of M&A activity observed during 2000 was probably due to relatively high company share values at the time, which tended to make M&A activity more palatable, as transactions can be largely or entirely financed by the exchange or issuance of shares. M&A activity reverted back to more baseline levels in 2001 and 2002. 2003 and 2004 saw the beginning of an increase in M&A activity in the drug delivery sector that has been maintained year on year up to 2007. Figures for 2008 up to the end of October show a dramatic drop in M&A activity. This is most likely due to the impact of the global economic downturn. Large falls in stock markets worldwide leave many small companies in a difficult position with greatly reduced market capitalisation. Many larger cash rich companies may be riding out the market volatility and will recommence M&A activity once stability returns. This could mean a bleak outlook for the remainder of 2008 and into 2009.



**Figure 2 – Drug delivery mergers and acquisitions (1997– October 2008).**

Source: PharmaDeals® v2 Agreements Database.



**Figure 3 – Effect of controlled release formulations.**

Slow release (purple line) vs traditional oral formulations (black line) of drugs may maintain plasma drug concentrations within a therapeutically beneficial window and avoid toxicity problems.

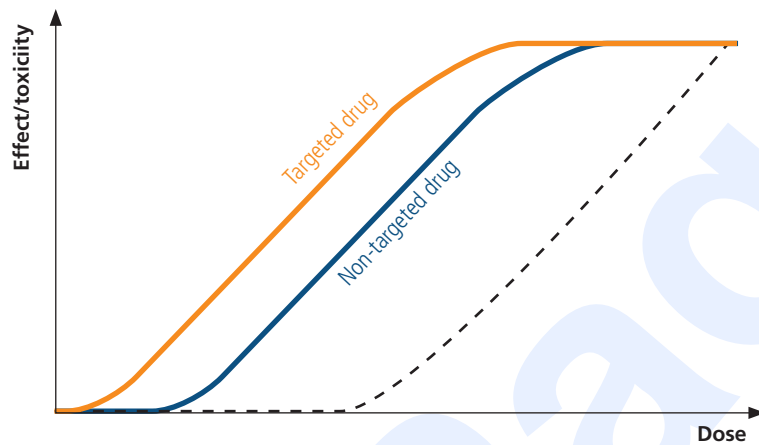
Drug targeting in particular can tilt the TI of a drug towards therapeutic benefit. There are several technologies currently in development that increase the efficacy of medication regimes. Drug targeting offers two inter-dependent benefits over non-targeted versions of the same drug:

- An increase in local concentration of the drug at the site of action; and
- A decrease in whole body concentration of the drug for any given dose.

The overall effect of these two benefits is therefore:

- Lower doses of a drug achieve the same therapeutic effect (reducing toxicity); and
- Higher doses of the drug may be administered without causing toxicity (which may result in increased efficacy).

The treatment of cancer is one area where the TI of a compound is particularly relevant. Cytotoxic compounds and/or radiation therapy have detrimental consequences when administered at therapeutic levels (e.g. nausea, hair loss, additional cancers). As outlined in Figure 4, the traditional doses of chemotherapeutic agents required to achieve maximum effect (the x-axis) are high enough to inflict a toxic effect upon a patient. Consequently, the regime of choice is nearly always a trade-off between toxicity and benefit.

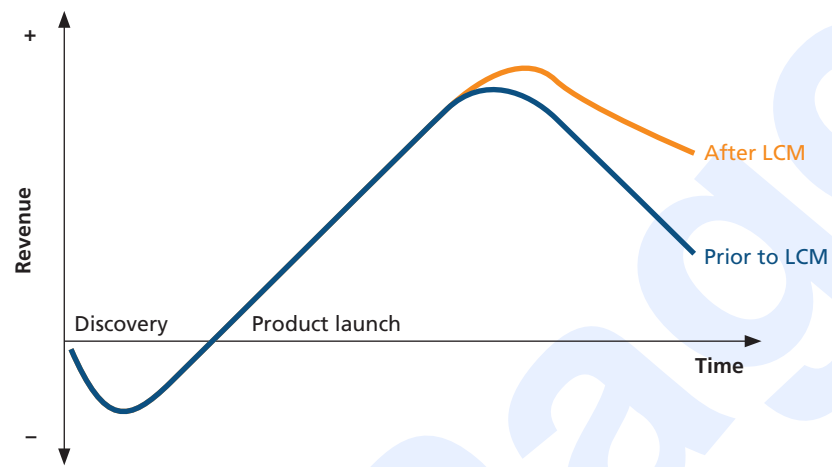


**Figure 4 – Doses of chemotherapeutic agent required to achieve maximum effect.**

Effect (solid lines) vs toxicity (dashed lines) profiles for 'Non-targeted' and 'Targeted' drug administration of the same drug. (The x-axis represents increasing doses of drug and the y axis an arbitrary scale of 'effect' or 'toxicity'.)

Innovative techniques that target therapies are in development today which will increase the dose of the therapy at the site of action, but lower the overall dose needed and therefore the systemic side effects. Examples of these types of technologies from Abraxis, University of California and Case Western are given below. It will only be a matter of time before the latter of these examples are in routine use.

- Doxorubicin nanoparticles have shown a 15-fold increase in drug efficacy with few side effects compared to the free therapeutic, which has limited efficacy due to cardiotoxicity.
- Abraxane® from Abraxis is paclitaxel bound to albumin particles for the treatment of breast cancer. This has shown up to double the efficacy and significant improvements in patient convenience.
- Research at Case Western is using gold nanoparticles coated with a photodynamic chemotherapeutic. Animal models have demonstrated faster localisation of drug (hours versus days). This, coupled with light activation only at the tumour site, gives scope for a wider TI and less patient inconvenience.
- Use of red blood cells as drug encapsulation devices by the French company, Erytech.



**Figure 6 – Life cycle management.**

products, its revenues fall. The deployment of a successful LCM project, however, can curtail this descent and generate additional revenue; defined in this situation as the area between the two curves. LCM thus offers the potential to increase cost-effectively either the life cycle of a drug beyond its normal 20 year period of exclusivity or, in some instances, increase the earnings within a single life-time. 30% of FDA drug approvals between 2006 and 2007 were for line extensions.<sup>44</sup>

LCM also involves the development of products for new indications, although not necessarily employing a new delivery technology. It is common practice that while a drug may initially be marketed for a specific indication, further research proves that it also has therapeutic value for other indications. For example, Eli Lilly has achieved approval for multiple indications for its drug Cymbalta® (duloxetine). The drug was approved in 2004 for the treatment of depression and achieved sales of US\$519M in the second quarter of 2007. Lilly filed a supplemental drug application for fibromyalgia.<sup>45</sup>

A further notable example of achieving LCM of a very old drug is thalidomide. Everyone is aware of the negative impact of this drug in pregnant women and its subsequent removal from the market in 1962. It is currently approved for newly diagnosed multiple myeloma. There are currently 15 trials evaluating the use of thalidomide either alone or in combination with other drugs for newly diagnosed, refractory and relapsed multiple myeloma.<sup>46</sup>

Reformulation has become an almost ubiquitous product life cycle strategy. The top 50 manufacturers used reformulation for almost two thirds of product launches during 2002–2005. However, JP Garnier, the former CEO of GSK expressed the view early in 2008 that the days of line extensions were numbered.<sup>47</sup> Cardiovascular, central nervous system, diabetes and women's health treatments have seen the most reformulation activity with significant efforts also in alimentary and metabolic drugs.

<sup>44</sup> <http://www.nature.com/nrd/journal/v7/n3/full/nrd2531.html>

<sup>45</sup> <http://www.fiercepharma.com> April 2007

<sup>46</sup> US Pharmacist July 2008.

<sup>47</sup> <http://www.guardian.co.uk/business/2008/feb/08/glaxosmithklinebusiness.pharmaceuticals>

## Commercialisation Strategies

	Risks	Benefits/returns	Resource implications
<b>Divestment</b>	None	No investment needed, little return	None
<b>Licensing</b>	Some legal risks	Low investment required, moderate returns (unless patent position very strong)	Few resources must be provided internally
<b>Service offering</b>	Low risk	Control of proprietary systems, low future returns	Resources must be provided internally
<b>Strategic alliance</b>	Informal structure creates risks	Flexibility	Permits pooling of resources & capabilities from more than one firm
<b>Joint venture</b>	Risks shared. Potential for partner disagreement or culture clash	Investment shared, larger potential returns than simple licensing	As for strategic alliance, less flexibility to vary inputs
<b>Internal commercialisation</b>	High investment requirement with associated risks	Increased control, larger potential returns	All resources required must be provided internally

**Table 6 – Strategies for the exploitation of innovation.**

Which of these strategies that will allow an innovator to appropriate the most return and provide the most acceptable risk/reward ratio mainly depends on:

- The characteristics of the technology;
- The extent of protection through IP; and
- The resources and capabilities of the innovator.

Effective patent protection is usually available for drug delivery technologies as is the need to access the complementary resources that drive the choice of strategy - although raising sufficient funds in the prevailing economic conditions may be challenging. As the scope and scale of resources available to a firm are so important to the choice of strategy, the strategy adopted for the commercialisation of a drug delivery technology at a given point in time may vary.

In the biotechnology industry, a two-stage model for innovation is common. Initially, new technologies may be developed internally by a small, research-intensive start-up. Once the technology has been developed to a point at which significant additional complementary resources are required, however, one of the other strategies (often licensing) is then used. It is useful to note that this two-stage model has arisen because it offers a route for innovators, especially academic researchers, to appropriate a higher proportion of the benefits potentially emanating from an innovation than could be captured by licensing or outright sale of an invention while it is still at the laboratory prototype stage. This two stage model is also very prevalent in academia, a rich source of innovation, but almost totally lacking in the complementary components required for successful commercialisation.

own due to its resource constraints. All the resources necessary for the development and production of a commercial product or service and its marketing/sales would be contributed by the licensee. Of course, this is reflected in the value split to each party.

Out-licensing the technology to multiple companies will typically require that some basic research work and demonstration studies would have to continue inhouse. Although no major investments in additional capabilities may be necessary, substantial effort may be required to provide training and transfer of the technology to the licensees. In a situation where there is weak or absent patent protection and the majority of the intellectual property is held as know-how, this would be a risky strategy to pursue. Potential licensees will require substantial disclosure of methods and proof-of-principle studies, probably in their own laboratories before agreeing significant licence terms. In such a situation a service strategy could be more appropriate. This could transition to an acquisition or licensing strategy as the exploiter of the technology becomes more comfortable and possibly even strengthens the IP position with the filing of additional patents.

If the product of a company is to be a *device*, this implies a strategy of internal commercialisation and a supplier business model. The device will ideally be applicable to the delivery of multiple different drugs with minimal or no customisation required. Interaction with pharmaceutical customers would be much less formalised than in the collaborative model and, rather than develop drug and device in tandem, the device would be customised to the needs of a drug formulation that has been developed independently.

By providing a service offering charged on a fee-for-service basis, the innovator would be able to maintain tight control of its know-how and receive early cash flow. Milestone payments could also be receivable based on technical milestones.

Two very different strategies and business models are compatible with the concept of the drug delivery company's product being a new pharmaceutical product. Both can permit the drug delivery company to appropriate a greater proportion of the overall return to the technology than it could do through the other product offerings, but both will require substantial investment in resources and capabilities by the drug delivery company. A product offering, based on collaborations with partner companies, clearly illustrates a collaborative business model and can be viewed as a strategic alliance. Depending on the degree to which the technology originator is willing to accept risk, the potential returns could be moderate or quite substantial.

An extreme form of the collaborative model would be an exclusive, long-term joint venture with a major pharmaceutical company. This may limit the resource contribution required from the technology innovator, thus reducing the risks involved, although the returns would be reduced accordingly. However, pharmaceutical companies are unlikely to pay a significant premium for exclusive access to an early stage technology that may only be applicable to some of their