

Drug Delivery: Past, Present and Future

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Introduction

Drug delivery is one of the fastest growing sectors in the pharmaceutical industry and an area in which effective deal making is essential for survival and growth. Many smaller 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.

Effective deal making is particularly important in the present economic climate. The general downturn in equity markets over the past couple of years has significantly weakened public share offerings as a means of raising the money that is required for rapid growth of drug delivery companies. Indeed, the NASDAQ biotech index fell by 45% during 2002¹ and the market for IPOs all but evaporated. However, the index had recovered to 80% of its 2001 value at the end of 2003. Nevertheless, companies have been increasingly reliant upon the development of strategic alliances for gaining access to the funds that are required for product development and corporate expansion.

The pharmaceutical sector has historically maintained strong earnings growth in the range of 10-15%. Such growth has been maintained not only by launching new products at a rate of 2-3 per year per company, but also by life cycle management of older products, which is playing an increasingly important role. As revenues from a drug can drop by up to 70% once its patent protection expires, if there is any way of adding new life to the product, life cycle management may help to protect brand sales².

Drug delivery is a way of improving the delivery characteristics of both marketed and developmental products, and adds value by increasing patent life or allowing the development of products that would not have been viable without a delivery/formulation system. In addition to life cycle based advantages, drug delivery technologies have many clinical advantages including control of drug concentration in the blood, improved safety and efficacy, improved patient compliance and ease of use, and expanded indications.

Pharmaceutical companies initially outsourced drug delivery to specialised companies, among the first of which were **Alza**³ and **Elan**. These companies initially specialised in oral and transdermal technologies and developed once-daily formulations or patches for both generic drugs and branded drugs for pharmaceutical partners. Most oral and transdermal drug delivery technologies are now generic and can be used by any company. This has led to generic companies such as **Mylan** and **Watson** developing and marketing drug delivery-improved generic drugs or super-generics. Alza and Elan, two of the then top drug delivery companies, soon realised that, if they wanted

to grow rapidly, in addition to developing new delivery technologies, they would have to start marketing their own drugs as the royalties received from their pharmaceutical partners were not sustainable long term.

Alongside Alza and Elan, new drug delivery companies were starting at a rapid rate. Taking a marketed drug and improving its delivery characteristics in return for single-digit royalty represents a much lower risk model than a biotechnology company developing a new chemical entity (NCE) from scratch that only has perhaps a 1 in 50 chance of reaching the market. Indeed, the cost of reformulating an existing drug for marketing is about US\$10-50 M, whereas the average cost of successfully developing an NCE is US\$802 M⁴. This latter figure includes the cost of project failures and the impact that long development times have on investment costs.

The 1980's saw a groundswell of new drug delivery companies focusing on technologies that may now be seen as routine. Transdermal drug delivery companies such as **Ethical Holdings**⁵, **Cygnus**⁶ and **Noven**, nasal delivery companies including **Ribogene**⁷ and **Nastech** and liposomal drug delivery companies such as **The Liposome Company**⁸, **NeXstar**⁹, **Liposome Technology**¹⁰ and **Fountain Pharmaceuticals** were established. Of these companies, only The Liposome Company and NeXstar achieved significant success.

With the development of biotechnology, new challenges and opportunities in drug delivery have arisen. Biotechnology has enabled the development of a new generation of biopharmaceutical products based on proteins, peptides and nucleic acids (termed macromolecules). Macromolecules present significant challenges to drug delivery because they are large molecules that frequently degrade rapidly in the bloodstream, have limited ability to cross cell membranes and generally cannot be delivered orally due to degradation in the gastro-intestinal tract. As a result, most biopharmaceuticals must be administered by injection, often multiple times per day or per week to obtain adequate efficacy. A new generation of drug delivery companies is now pursuing the improvement of macromolecule delivery with the aim of non-parenteral

¹ The year end NASDAQ biotech index was 908.79 and 724.1 in 2002 and 2003, respectively.

² Text adapted and updated from The Drug Delivery Companies Report 2001, PharmaVentures Ltd.

³ Alza was acquired by Johnson & Johnson in March 2001.

⁴ Tufts Center for the Study of Drug Development, November 2001.

⁵ Now Amarin Corporation.

⁶ Now divested of its drug delivery technologies and focusing solely on glucose monitoring devices.

⁷ Acquired by Cypros in November 1999, the joint company is now called Questcor.

⁸ Acquired by Elan in May 2000.

⁹ Acquired by Gilead in July 1999.

¹⁰ Changed its name to Sequus and was then acquired by Alza in March 1999.

delivery. Technologies at the forefront of non-parenteral macromolecule delivery are inhaled and needle-free technologies. Depot technologies are also focusing on macromolecule delivery although this involves the parenteral administration of sustained-release formulations.

The Current and Evolving Market

Predictions of future growth, and indeed approximations of the current market size, vary according to source. However, of the current US\$355 B global pharmaceutical market¹¹, as much as 13%¹² is believed to be accounted for by sales of products incorporating a drug delivery system, or about US\$46 B. The drug delivery market has been predicted to grow at a compound annual rate of 10% per year over the next few years¹³. Others anticipate that the total drug delivery market will be worth an estimated US\$120 B by 2007¹⁴.

CMR International¹⁴ estimated that 15% of pharmaceutical company R&D budgets in 2001 was to be spent on projects incorporating a drug delivery system. The percentages of such projects that utilise each of the available routes of drug delivery are: oral, 47%; pulmonary, 16%; transdermal/topical, 11%; subcutaneous/intramuscular, 11%; intravenous, 7%; and other, 8%.

Of such R&D drug delivery projects, only about 40% focused on novel compounds in development, the remainder being focused on already-marketed products. This demonstrates that there is much greater emphasis on the application of drug delivery technologies to existing compounds as opposed to NCEs.

According to analysts **UBS Warburg**¹⁵, sales of drug delivery-based products are expected to be strong over the next few years, with new product launches across all technology platforms reaching US\$30 B in sales by 2005. Oral drug delivery leads, with anticipated sales that are expected to double to US\$18 B by 2005, an annual growth rate of 14%. Pulmonary delivery products are expected to reach sales of US\$6 B by 2005, increasing from about US\$2.5 B in 1999. Implantable depot technology is expected to be the fastest growing sector, with an annual growth rate of 17% and sales of US\$3 B by 2005. Transdermal drug delivery, currently at about US\$1 B sales, is reaching maturity and annual growth is not expected to exceed 11% annually through to 2005. Other drug delivery routes such as intrathecal and transmucosal may add a further US\$1 B in sales by 2005.

The Current Players

The drug delivery sector comprises a broad spectrum of over 300 companies¹⁶. Thirty-one of which are listed in Table 1. The revenues of these listed companies had 2002 cumulative totals of US\$3.4 B, a 30% increase over 2001 revenues of US\$ 2.7 B. Only **Biovail** and **Andrx** reported revenues of over US\$500 M in 2002, and these two companies represent almost 50% of the total revenues from the companies listed in Table 1. There is a broader middle tier of companies including **Lavipharm**, **KV**,

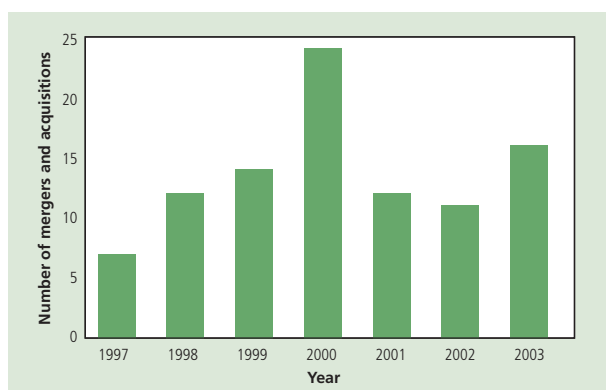


Figure 1 – Drug delivery mergers and acquisitions, 1997–2003. Source: PharmaDeals® Agreements

Kos, **NexMed**, **Bespak**, **SkyePharma**, **Eurand**, **Nektar**, **Noven** and **Connetics**, each with 2002 revenues of US\$50-500 M.

M&A Activity

Traditionally, drug delivery companies could be broadly categorised into either specialist technology providers or cross platform providers. Specialist technology providers offered drug delivery solutions in a single delivery area, for example needle-free delivery, whereas cross platform providers offered a range of delivery technologies over a variety of delivery areas.

To remain competitive, specialist technology providers need to offer leading-edge technologies. However, due to their narrow specialisation, these companies are at a constant risk of external supercession. M&A activity enables these companies to both maintain a technological advantage and to broaden their technology platforms within a single delivery area, and so offer more complete delivery solutions. For example, through its acquisition of **Southern Biosystems** (SBS) in April 2001, Durect gained access to SBS's SABER depot delivery system in addition to microsphere and drug loaded implant technologies. Durect itself is focused on the extended delivery of drugs, principally through its DUROS® implant technology.

Drug delivery companies are facing a trend of major pharmaceutical companies wanting to interact with "one stop shops". Cross platform providers are able to use M&A to broaden their technology capabilities and expand into new delivery areas. An example of such an acquisition was Nektar Therapeutics' acquisition of Shearwater Polymers in July 2001, a company specialising in PEGylation technology. The acquisition had a value of US\$191 M, of which US\$72.5 M was paid in cash and the remainder in Nektar stock. This acquisition followed Nektar's previous acquisition of Bradford Particle Design in January 2001 for US\$200 M, of which US\$20 M was in cash and

¹¹Source www.gsk.com

¹²The Application of Novel Drug Delivery Systems. CMR International, April 2001.

¹³CIMA Labs, Inc., 424B4 SEC filing, November 2000.

¹⁴Drug Delivery Systems: Technologies and Commercial Opportunities, Decision Resources, November 1998.

¹⁵UBS Warburg, 1999, as presented in Med Ad News, June 2000.

¹⁶An approximation derived from PharmaVentures' Drug Delivery Companies Report 2002/03, PharmaVentures Ltd, and internal PharmaVentures resources.

Company	Revenue US\$ M		Location	Web Site
	2002	2001		
Biovail Corp.	788.0	583.3	Mississauga, Canada	www.biovail.com
Andrx Corp.	770.9	749.0	Davie, FL	www.andrx.com
Lavipharm SA	288.2 ¹⁸	260.2 ¹⁸	Peania Attica, Greece	www.lavipharm.gr
KV Pharmaceutical Co.	245.0	204.1	St Louis, MO	www.kvpharmaceutical.com
Kos Pharmaceuticals, Inc.	173.0	91.0	Miami, FL	www.kospharm.com
NexMed, Inc.	148.0	68.1	Robbinsville, NJ	www.nexmed.com
Bespak plc	125.4 ¹⁸	103.9 ¹⁸	Milton Keynes, UK	www.bespak.com
SkyePharma plc	104.7	69.5	London, UK	www.skyepharma.com
Nektar Therapeutics	94.8	77.5	San Carlos, CA	www.nektar.com
Eurand International SpA ¹⁹	89.4 ¹⁸	74.9 ¹⁸	Milano, Italy	www.eurand.com
Noven Pharmaceuticals, Inc.	55.4	45.9	Miami, FL	www.noven.com
Connetics Corp.	52.8	34.1	Palo Alto, CA	www.connetics.com
Alkermes, Inc.	47.3	54.1	Cambridge, MA	www.alkermes.com
CIMA Labs, Inc. ²⁰	46.6	32.0	Eden Prairie, MN	www.cimalabs.com
Penwest Pharmaceuticals Co.	42.0	40.0	Patterson, NY	www.penw.com
Bentley Pharmaceuticals, Inc.	39.1	26.4	Exeter, NH	www.bentleypharm.com
Aradigm Corp.	29.0	28.9	Hayward, CA	www.aradigm.com
Atrix Laboratories, Inc.	26.4	15.8	Fort Collins, CO	www.atrirlabs.com
Matrixx Initiatives, Inc.	25.2	20.5	Phoenix, AZ	www.matrixinc.com
Impax Laboratories, Inc.	24.5	6.6	Hayward, CA	www.impaxlabs.com
Flamel Technologies SA	21.0	13.1	Venissieux Cedex, France	www.flamel.com
ML Laboratories plc	19.9	13.9	Warrington, UK	www.mllabs.co.uk
Novavax, Inc.	15.0	24.1	Columbia, MD	www.novavax.com
Profile Therapeutics plc	12.7	11.8	West Sussex, UK	www.profiletherapeutics.com
Iomed, Inc.	12.1	11.7	Salt Lake City, UT	www.iomed.com
Columbia Laboratories, Inc.	9.4	2.1	Livingston, NJ	www.columbialabs.com
Nastech Pharmaceutical Co.	8.9	2.6	Bothell, WA	www.nastech.com
LecTec Corp.	6.8	14.9	Minnetonka, MN	www.lectec.com
Scolr, Inc.	6.5	8.2	Redmond, WA	www.scolr.com
Durect Corp.	6.3	6.1	Cupertino, CA	www.durect.com
AP Pharma, Inc.	4.0	3.2	Redwood City, CA	www.appharma.com
Total	3338	2698		

Table 1 – Publicly quoted speciality pharmaceutical companies that focus on drug delivery¹⁷.

US\$180 M in Nektar stock. Bradford Particle Design added supercritical fluid drug formulation technology to Nektar's platform. Nektar's now broadened drug delivery and development capabilities are the reason that the company changed its name from Inhale Therapeutics Systems in January 2003.

M&A is thus a well-trodden strategy amongst both specialist technology and cross platform providers in the drug delivery sector. Figure 1 illustrates the level of M&A transactions amongst companies where at least one party had a focus on drug delivery. The peak 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 was considerably less both before and after 2000.

Additionally, some drug delivery companies have adopted a strategy to evolve as integrated drug delivery/pharmaceutical companies. M&A provides drug delivery

companies with a method of vertically integrating in this way. Such vertical integration ultimately leads to revenue, generated through the sale of proprietary therapeutics in addition to revenues obtained through partner-sponsored programmes.

Elan is one such company to make significant progress down the route of becoming an integrated pharmaceutical company via M&A activity. Elan's acquisitions have focused on the therapeutic areas of neurology and pain management and have encompassed drug delivery technologies including transdermal, nanoparticle, liposomal and protein/peptide drug delivery technologies. Elan grew rapidly during the late 1990's and had revenues of US\$1.7 B in 2001, up from US\$1.3 B in 2000. Elan's shares traded at US\$40-60 for most of 2000 and 2001.

However, Elan's fortunes changed during 2002. In January of that year, The Wall Street Journal raised

¹⁷Compiled from company annual reports.

¹⁸Calculated using average exchange rate for year.

¹⁹Eurand is a private company, not public.

²⁰Cephalon announced in November 2003 that it plans to acquire CIMA Labs.

concerns about Elan's accounting practices detailing how the company allegedly boosted its revenues by setting up dozens of off-balance-sheet joint ventures. There was also a major problem in clinical tests for Elan's Alzheimer's drug. During the course of the year, Elan's share value effectively collapsed. Elan subsequently undertook an extensive recovery programme. As a result of this Elan has sold off a number of subsidiaries to pay debts.

Other key deal activities that were announced in 2003 relating to mergers and acquisitions included Watson's acquisition of **Amarin Development**, **Aradigm's** acquisition of **Weston Medical's** assets and the announcement that **Cephalon** was to acquire **CIMA Labs**. There was also an announcement of a merger that was subsequently terminated between NPS and Enzon.

Watson's October 2003 acquisition of Amarin Development, a wholly owned subsidiary of the Amarin Corporation, gave Watson access to a number of patented, oral controlled release drug delivery technologies. It also gave it access to products in development including glipizide extended-release tablets for type-2 diabetes, for which Watson received approval on the 5 mg strength formulation in September 2003.

In February 2003, Weston Medical, a UK based drug delivery company, entered administration after it announced 5 months earlier that there was to be a delay in the first launch of the Intraject drug delivery technology. Problems arose during internal clinical trials leading to the need for alterations in the design of the Intraject device. Weston Medical entering into administration allowed Aradigm to purchase selected assets of Weston Medical for approximately US\$2 M cash, including test and production equipment, intellectual property and other assets. The development of the Intraject system is now continuing with Aradigm, where the technical difficulties seen by Weston Medical appear to have been overcome.

The initial announcement relating to CIMA was made in August 2003, whereby aaiPharma was to acquire CIMA Labs with an estimated total deal value of US\$350 M. However, this agreement was terminated in November 2003 resulting in a termination fee of US\$11.5 M payable by CIMA to aaiPharma. The termination occurred due to the announcement that Cephalon had signed a definitive merger agreement under which Cephalon will acquire all outstanding common shares of CIMA. The total value of the transaction was said to be in the region of US\$515 M. This acquisition is expected to be completed in the first quarter of 2004.

A further terminated merger was that between **NPS Pharmaceuticals** and **Enzon Pharmaceuticals**. These two companies initially announced that they were to merge in February 2003 in a stock-for-stock transaction with a value of approximately US\$1.6 B. In April, it was announced that the legal requirements for the merger had been satisfied and the merger was then expected to be completed.

However, in June, NPS and Enzon terminated the merger agreement following a determination by NPS that it wanted to renegotiate the original stock conversion

ratio, but Enzon did not believe there was any basis for renegotiation. NPS paid a termination fee to Enzon in the form of 1.5 M shares of common stock.

Future Market Challenges

With the exception of the past 20 years or so, drug discovery and manufacturing practices have favoured the development of small molecules as the predominant product form of drugs within the pharmaceutical industry. Small molecules have a clear advantage where oral bioavailability is sufficient to deliver an efficacious quantity of drug to patients. There is thus a strong and arguably justified comfort factor within the mindset of pharmaceutical company executives that, all else being equal, small molecules are the best first option when selecting drug candidates. This mindset is unlikely to change in the near term and there remains a strong technological focus on small molecule development via technologies such as combinatorial chemistry and high-throughput screening.

Macromolecules represent one of the future horizons for drug development. For example, the worldwide market for recombinant biopharmaceutical compounds amongst the top 200 selling prescription drugs grew from about US\$19.8 B to US\$25 B, or 24%, between 2001 and 2002 (sales for 2001 and 2002 are presented in Table 2). This compares favourably with an increase of 10% amongst the entire top 200 selling prescription drug market from about US\$178 B in 2001 to US\$194 B in 2002²¹.

Conclusion

The drug delivery sector represents a dynamic, rapidly evolving sector as companies continue to vie for positions that will maximise commercial returns. Both markets and technologies continue to drive the sector, and it will be interesting to witness its evolution over the ensuing years. The timeline for evolution is likely to be decades rather than years due to the emergence of novel technologies that provide new drug delivery solutions.

²¹Modified from Med Ad News, May 2003.

This article is taken from a PharmaVentures/PharmaDeals publication: Effective Licensing & Commercialisation of Drug Delivery Systems 2004. For further information, or to purchase a copy, please contact:

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