Delivering biotherapeutics – technical opportunities and strategic trends

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Abstract

As the list of biological drugs gaining regulatory approval grows, this paper examines how different technological approaches to delivering these drugs have evolved, and how business strategies have developed to meet the challenges. Companies can broadly be divided into three segments based on their technological approach: (1) developers of novel devices, (2) exploiters of new routes for drug administration and (3) reformulators of drugs. Case studies of companies in each segment are presented. The paper concludes by suggesting that further consolidation of the drug delivery sector is likely either between smaller companies or between large pharma and smaller entities. It is also argued that, as competition intensifies, drug delivery should no longer be regarded as a 'bolt-on', but integrated at an earlier stage of the product life cycle.

INTRODUCTION

The field of drug delivery – the way in which drugs are administered and the dosage form used – is witnessing an innovative acceleration as companies seek to capture the future promise of biotherapeutics and differentiate themselves in a crowded market.

Injection remains the most effective way of administering macromolecular therapeutics such as hormones, growth factors, monoclonal antibodies and vaccines. Delivering these drugs using more 'patient-friendly' routes than injection, while maintaining drug efficacy is fast becoming the 'holy grail' of drug delivery. This paper focuses on innovations in parenteral (injection), pulmonary (inhalation) and oral drug delivery of therapeutic biologicals. It argues that there is still a deficit of winning technological solutions to biological drug delivery, hence major opportunities for innovation exist. The sector is also experiencing flux as the industry structure becomes realigned to deal with risks and growing opportunities, and this paper examines various trends that point to consolidation setting in. It also argues that drug delivery should no longer be regarded as a 'bolt-on' considered only towards the end of a product's patent expiry, but needs to be strategically integrated as part of the whole life cycle of the product.

DRIVERS AND OPPORTUNITIES FOR BIOLOGICAL DRUG DELIVERY

The number of biological drugs approved by the Food and Drug Administration (FDA) has been rising steadily since 1981, when the FDA first approved recombinant human insulin.[1] In 2000, over 30 biotechnology drugs and vaccines were approved (see Figure 1).[2] The number has now reached 'critical mass', presenting a growing opportunity for drug delivery players to provide technical solutions to the challenges of macromolecular delivery. These challenges arise from a fundamental of physiology: after drugs enter the body they undergo the pharmacokinetic processes of absorption, distribution, metabolism and excretion (ADME).

When ingested most proteinaceous

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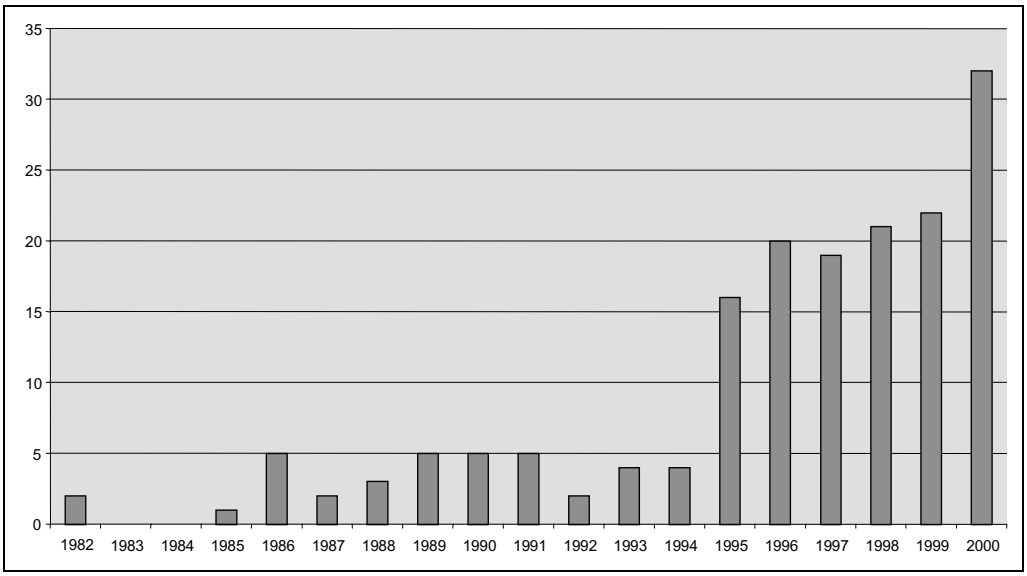

Figure 1: Biotechnology drug and vaccine drug approvals (source: Biotechnology Industry Organization)

Oral delivery of protein drugs-first pass metabolism

molecules are partially or completely denatured by the acid pH of the stomach and subsequently broken down in the gut. Blood from the digestive system passes via the portal system to the liver where drugs can undergo further metabolic breakdown – this is the effect of first pass metabolism. Moreover, even if molecules were to survive this process, the relatively large size of most biotherapeutic molecules means they are only poorly absorbed through cell membranes. Demonstrating sufficiently high bioavailability of biologicals in the patient's bloodstream to cause a therapeutic effect, other than by traditional needle and syringe injection, has proved to be a major barrier for the pharmaceutical industry. This has created an opportunity for the specialist drug delivery sector to provide a range of technical solutions.

EMERGENCE OF INDUSTRY SEGMENTS BASED ON TECHNOLOGY

Advances in drug delivery facilitate product differentiation

Logically, there are three options to overcoming the barriers to biologicals delivery and drug delivery companies are actively exploring some or all of these approaches in the race to differentiate their product offerings from their competitors. These three groups of approaches can be summarised as follows:

- **Segment 1:** developers of novel devices for biotherapeutic drug delivery (eg for injection or deep lung delivery).
- **Segment 2:** exploiters of new routes of administration (eg deep lung, nasal membrane) typically in combination with a novel delivery system or technology.
- **Segment 3:** reformulators of the therapeutic using novel chemistries and physicochemical technologies for an existing or new route of entry (eg oral).

Businesses in Segment 1 include those developing needle-free technologies (see Table 1). Their strategy is based on the view that parenteral delivery of biologicals has a number of therapeutic advantages, not least in relation to bioavailability and accurate dosage control. If some of the issues relating to the use of needles such as patient phobia, risks of needlestick injury and difficulty of self-administration can be overcome – as the needle-free technologies claim – then there is

Table 1: Status of industry segments based on technology

	Liquid needle-free	Inhalation	Oral
Device development (Segment 1)	Technical development required	Technical development required	No development requirements
New route for macromolecules (Segment 2)	No development requirements	Technical development required	Technical development required
Reformulation (Segment 3)	No development requirements	Technical development required	Technical development required
Bioavailability	High – delivered directly into blood stream	Medium – dependent on effective delivery to deep lung	Low – first pass effect
Development risk	Medium/low	High	High
Stage of development	Approved	Phase III (insulin)	Phase III (Heparin)
Examples of companies	Weston Medical, Bioject, Antares Pharma	Inhale Therapeutic Systems, Vectura, Aradigm, Elan	Elan, Eurand, Emisphere

Low development risks associated with liquid, needle-free injection

enormous potential for delivering a range of biotherapeutics. For liquid needle-free technologies, a further attraction is the relatively lower development risk where the technological hurdles relate to device development rather than reformulation of the therapeutic itself.

The alternative to a liquid formulation is the delivery of a powder. A key attraction of dry powders is the improved stability of the drug in ambient temperatures. Powderject Pharmaceuticals Plc went down this route and for a while was a leader in developing dry powders alongside suitable devices to deliver the material. Recently, however, the company has refocused its activities away from reformulating existing drugs as powders, instead licensing out certain of its technologies to a partner (the reformulation adds major new development hurdles and can significantly lengthen product time to market).

Whether the drug is a dry powder or a liquid, needle-free injection devices work on the principle of delivering a burst of drug that penetrates the outer layers of the skin to reach capillaries, using a stored energy source to deliver a given volume of drug when the device is triggered. The system is potentially more applicable for patients who require regular administration of a biological drug that might typically be administered with a needle and syringe. The drug administration process is simplified and can, as a result, improve patient compliance and enable self-administration, reducing the burden on primary and secondary care resources.

In relation to liquid delivery, Bioject, founded in 1985, was one of the first drug delivery companies to commercialise a needle-free delivery technology. Bioject's first generation product was low cost and reusable. A number of companies now offer similar products, including Mediject and Equidyne. These systems are attractive for the delivery of low-cost biological drugs where multiple administrations are needed, and Bioject has been successful in marketing its first generation product for insulin self-injection in the home.

The success of biotherapeutics such as growth factors, monoclonal antibodies and cytokines has presented needle-free delivery companies with the opportunity to develop next-generation products to expand their technological and product

CASE STUDY 1 – WESTON MEDICAL PLC

Weston Medical, founded in 1994, is a platform delivery company offering a 'service' to pharma and biotechnology companies, giving them the opportunity to license Weston's system for development and sale in combination with their therapeutic. Weston has responded to market demand by developing the Intraject®, a needle-free, pre-filled, sterile, fully disposable, single use device, designed to deliver high-value liquid biotherapeutics. The high cost often associated with drugs such as monoclonal antibodies and interferons can justify a higher unit cost delivery device to be used in combination, on the basis that the proportional cost of the device as part of the package is low, while the healthcare benefits are high. There is the additional attraction of product 'bundling' with a novel delivery technology that can help extend product patent life and potentially compete with generic versions of the molecule as they enter the market.

Higher 'unit-cost' device for the delivery of premium biotherapeutics

Weston Medical has signed a number of deals with influential global players such as Roche and Pharmacia, giving their partners access to Weston's device and a novel delivery route for their molecules. These deals have helped to give Weston credibility for its successful initial public offering (IPO) in 2000. Weston's 'high-value' strategy appeared to have paid off, with the company generating a market cap of US$325m at its IPO on the London Stock Exchange, significantly higher than similar needle-free delivery companies such as Bioject (market cap: US$43.5m) and Medi-Ject (market cap: US$7.5m) at that time.[3] Recently, Weston has announced deals in the vaccines and monoclonal antibody area, with Celltech (for influenza vaccine) and Cambridge Antibody Technology (CAT) (for monoclonal antibodies). With the increasing complexity of some biotherapeutics, such as monoclonal antibodies, it is unlikely that, in the near term, delivery solutions will be found to enable these molecules to be delivered in any way other than parenterally, providing Weston with significant potential licensing deal opportunities.

Weston Medical 'high-value' strategy

The huge surface area of the deep lung provides a route for systemic delivery of biotherapeutics

offerings to new high-value markets, whereby a higher per-unit cost delivery system can be justified.

Weston Medical, for example, has been a leader in adopting a strategy to target high value macromolecular drugs with their single-use, disposable liquid needle-free injection system. Weston Medical's strategy has been to partner with the pharmaceutical majors as Case Study 1 illustrates.

Companies in Segment 2 have taken a fundamentally different path, instead making the assumption that significant market share can be won through using alternative delivery routes for macromolecules when compared with the parenteral route (see Table 1). Currently, most potential is offered by pulmonary delivery, ie inhalation of drugs to the deep lung. Although unlikely to be as therapeutically effective as injection, inhalation has the potential to achieve good bioavailability owing to the large surface area of the deep lung. Problems associated with the absorption of macromolecules across cell membranes are at least reduced because of the thinness of the air/blood barrier in the deep lung. In addition, the pH of lung fluid is similar to that of blood, eliminating the problem of protein breakdown, associated with oral delivery.

Pulmonary delivery requires a high level of innovation and product development: not only does success depend on an effective delivery device, but it also requires a degree of drug reformulation from the standard freeze-dried or liquid form, to create drug particles suitable for inhalation to the deep lung (effective inhalation requires that drug particles must typically meet a size range of 1–3 μm diameter[4]). As a result there are higher risks associated with its development compared with needle-free injection of un-reformulated biologicals.

Modern inhalation technology devices and formulations enable a controlled 'cloud' of drug to pass efficiently along the airways, into the deep lung, where the alveoli provide a huge surface area of thin

cellular membrane through which the drug particles can be absorbed directly into the bloodstream.

There has been a great deal of interest in this area from pharma and biotechnology companies looking to differentiate their products and extend product life cycles, and various biotherapeutics have been considered as good candidates for inhalation, including insulin, interferon and human growth hormone. Inhale Therapeutic Systems is a good example of a company active in this field, regarded by many as a leader in the race for commercialisation, collaborating with Pfizer to produce a systemic delivery system for insulin via the deep lung. Diabetes is a hugely attractive and growing market where needle and syringe delivery and pen injectors predominate and where there is large unmet demand for less invasive delivery modes. Inhale and Pfizer's programme completed Phase III clinical trials in June 2001.

Crucial to an effective device are factors such as actuation/trigger mechanisms, and dispersion of the drug from the device to ensure that a sufficient volume of drug reaches the deep lung, and is not deposited in the device, or in the mouth and upper airways. Systems such as the Inhale device, SPIROS® (Dura/Elan), AERx® (Aradigm) and AERODOSE® (AeroGen) have all been developed specifically to enable systemic delivery via the pulmonary route. Alongside the device, effective delivery depends on effective formulation. Research in this area attempts to formulate dry powders of an ideal stability, size and shape to promote efficient delivery. The importance of system versus formulation is often debated; in reality the key to success is the combination of effective formulation and device.

Successful pulmonary delivery depends on a combination of effective device and drug formulation

Building on its inhalation technology platform, Inhale Therapeutic Systems provides an interesting example of a company that has recognised the importance of formulation to the successful development of novel delivery systems (see Case Study 2).

High technical barriers associated with the successful oral delivery of macromolecules

CASE STUDY 2 – INHALE THERAPEUTIC SYSTEMS

Inhale Therapeutic Systems, founded in 1990, has pioneered systemic delivery via the deep lung. Inhale, like Weston Medical, has adopted a 'platform' strategy, offering pharma and biotechnology companies the opportunity to partner chosen drugs with the Inhale technology. However, Inhale, through acquisition, has integrated across the drug delivery value chain to create a multi-platform business. Inhale's first product offering was centred on a 'next generation' inhaler for systemic delivery. It has since added formulation expertise to its offering. PulmoSphere technology, acquired through Alliance Pharmaceutical Corp., is a particle formulation technology that creates a powder of hollow, porous, drug containing shells, of the required size for delivery via the deep lung.

Continuing with this strategy, its formulation capabilities and offerings have expanded beyond inhalation, in an attempt to become a provider of a range of drug delivery solutions to the biopharmaceutical industry. The Inhale 'family' of companies now includes Shearwater, bringing molecular engineering capabilities, and Bradford Particle Design plc, bringing powder processing capabilities for oral, injectable and other delivery mechanisms. This broadening of focus reflects an attempt to reduce the risks for the company associated with the development of inhalation technology. Throughout, maintaining a leading position in the delivery of macromolecules has remained key to the strategy.

Segment 3 companies have taken the strategic challenge of facing the problem of oral delivery 'head-on' aiming to overcome the physiological hurdles associated with first pass metabolism and bioavailability by altering the pharmacokinetic and pharmacodynamic properties of the biotherapeutics themselves. In our view, even higher technical barriers are associated with successful oral delivery of macromolecules than with either of the other two approaches described. Successful development in this area will not merely

have to overcome problems associated with resilience to first-pass metabolism, but will also have to ensure that the active drug is transported across cell membranes at the desired time and place. Because of the technical challenges, a truly effective solution to the oral delivery of macromolecules is even further from market success than systemic inhalation technology. A major clinical success in this area would be groundbreaking and pose a potentially significant threat to companies that have adopted the alternative strategies that we have discussed. The likelihood, however, owing to the wide range of classes of biologics and their relative instability, is that solutions in the oral area will need to be tailored for each drug – a single 'works for all' formulation technology is still a distant reality.

There have been some promising recent advances towards achieving successful oral delivery of macromolecules. For example, by altering the barrier properties of the cell membrane or the drug particle surface itself, degradation can be prevented and absorption across the small intestine can be improved. In addition, researchers have been experimenting with changing the route of transfer into the bloodstream to the large intestine, through delayed release mechanisms or by using site-specific coatings that disintegrate in the colon.

Companies with an interest in oral delivery of macromolecules include major players such as Elan and Eurand, and smaller companies such as Emisphere Technologies Inc. Emisphere is actively seeking solutions to enable the oral delivery of macromolecules. It has demonstrated its Carrier Mediated oral delivery technology for a wide variety of biotherapeutics in preclinical studies. Targets include insulin, calcitonin, human growth hormone, erythropoietin (EPO), interferon and heparin. This technology potentially overcomes the problem of limited absorption by exploiting the use of carrier molecules, which selectively and reversibly bind to form conformations of therapeutic proteins that can effectively pass through a cell membrane. Once across that membrane, the molecule can return to its original therapeutically active conformation. Through a collaborative joint venture with Elan Corporation PLC, Emisphere's most advanced product using this technology is oral heparin. Heparin is commonly prescribed against the risk of thrombosis following surgery. Heparin formulations, with a molecular weight ranging from 3,000 to 30,000 Da, are currently administered by injection. Oral delivery of heparin has the potential to improve patient compliance, and generally provides a simpler method of delivery to enable patients to self-administer at home.

Elan Corporation, despite its current share price drop, provides a good illustration of a fully integrated pharmaceutical company using its core expertise to tackle the problem of oral delivery of macromolecules. The company has created a multi-platform drug delivery offering in order to widen its product portfolio through extensive partnerings and acquisition (see Case Study 3).

Many macromolecule drug delivery technologies have yet to be proven commercially

THERE IS OPPORTUNITY MATCHED WITH UNCERTAINTY

The future for the biologicals drug delivery segment looks promising – fuelled by the expectation of new drugs emerging in the post-genomics era. More than 20 therapeutics, incorporating delivery systems, were approved or launched in 2001[5] but it is still the case that many macromolecule delivery technologies using novel routes and formulations have yet to be proven commercially. The drug delivery market is also dependent on the successful growth of the biotherapeutics market and the success of specific molecules currently in early development and clinical trials: thus there is both uncertainty and opportunity.

CONCLUSION

One possible scenario is that once winning technologies become more

CASE STUDY 3 – ELAN CORPORATION

Elan Corporation PLC has grown, both internally and through acquisition, to be a leader in the field of innovative drug delivery. Since it was founded in 1969, Elan has become a fully integrated pharma company, and a 'one stop' platform company for drug delivery. Historically, Elan's expertise has focused on oral delivery where it has established a strong research position in oral macromolecular delivery through its own proprietary technologies. One such technology, the Bio-erodible Enhanced Oral Drug Absorption System (BEODAS®), claims to be able to improve the oral bioavailability (level of drug delivered systemically) of peptides, proteins and other macromolecules. This is achieved through the entrapment of active drug in a range of sub-micrometre sizes within a biodegradable polymer matrix. This inert polymer protects the drug from degradation and improves absorption through increased surface area and altered chemical properties.

Like Inhale, Elan has diversified and following the acquisition of both a device company (Dura Pharmaceuticals) and a formulation company (Quadrant Healthcare plc) in 2000, Elan can now add inhalation expertise to its offerings.

obvious in the crowd, big pharma will be able to choose their preferred delivery technologies with more confidence. This may put increasing competitive pressure on the single platform companies. Businesses may have to diversify to survive.

Powderject PLC is an example of a single-technology drug delivery company who has diversified, shifting strategic focus towards becoming a fully integrated business in the vaccines market. This has been achieved through the ongoing success of a licence agreement with GlaxoSmithKline to develop DNA vaccines and the subsequent growth through acquisitions of integrated vaccines businesses, such as Celltech Medeva's vaccines division and SBL Vaccin (formerly a subsidiary of Active Biotech AB). In March 2002, Powderject sold its drug delivery business to AlgoRx, with a licence to the powder injection technology for drug applications outside the vaccines area.

Other platform companies such as Inhale have remained focused on drug delivery, but have acted to extend their technology portfolio to manage their risks and widen their offerings, while also capturing more of the value chain. It follows that consolidation is occurring and we are already witnessing this in two ways.

Firstly the larger and more well-established drug delivery players have acquired complementary technologies and businesses – in fact deals between two drug delivery companies accounted for five of the eight merger and acquisition deals in the drug delivery sector between 2000 and 2001. The highest value deals were conducted by Inhale, in acquiring Bradford Particle Design and Shearwater, with a combined value of over US$350m.[6] Secondly, we have witnessed big pharma integrating into drug delivery through acquisition. The attractiveness for big pharma is immediate access to technologies, markets and a reduction in royalty stacking that can otherwise dramatically erode revenues. Johnson and Johnson's merger with ALZA, worth a staggering US$10.5bn, may represent the beginning of a trend away from drug delivery 'service' companies, towards full integration of these technologies into the core of pharmaceutical businesses.

So, while once in the shadow of drug discovery, and regarded as a 'bolt on' to extend product life as patents expire, new drug delivery technologies in the biologicals area are finally being regarded as a crucial source of strategic advantage, potentially holding the key to success or failure in the clinic and the marketplace. Companies who leave it too late in the product life cycle to address the issue of drug delivery may find their competitors have got there first.

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