

## Biopharmaceuticals – Challenges and Opportunities Facing the Drug-delivery Industry

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### Abstract

The pharmaceutical industry – and in particular the biopharmaceuticals market – is growing fairly steadily. However, the application of novel drug-delivery technologies towards biologics has been somewhat limited. This article discusses the use of drug delivery to enhance protein and peptide therapeutics. Some products have been commercially successful while others have not. Therefore, life-cycle management issues that face drug-delivery-system (DDS)-enhanced biotherapeutics are examined, and the article offers examples of drug-delivery technology that is currently being implemented to reformulate and improve biopharmaceuticals.

### Keywords

Drug delivery, biopharmaceuticals, biologics, polyethylene glycol (PEG)-ylation, half-life, targeting, burst effect, life-cycle management

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As a whole, the pharmaceutical industry has been commercially successful over the years. In 2008, the global pharmaceutical market increased by 4.8% to surpass US\$770 billion.<sup>1</sup> An analysis by Technology Catalysts International (TCI) estimates that sales of biopharmaceutical therapeutics<sup>2</sup> accounted for approximately 12% of the entire market, with sales poised to reach US\$100 billion before 2010.

As shown in *Figure 1*, the numerous commercialised biotherapeutics can be categorised into several groups. Based on worldwide sales, the 25+ launched antibody therapeutics account for the largest segment, followed by erythropoietin (EPO) and insulin. All three areas have seen steady growth over the past decade and their combined revenue accounts for nearly three-quarters of the biopharmaceutical market.

By examining the individual product formulations within the biologics market, one will notice a lack of novel drug-delivery-system (DDS) applications. This is especially true compared with the rate of commercialisation within the small molecule drug-delivery industry. While the overall drug-delivery market exceeds US\$100 billion globally,<sup>3</sup> DDS-enhanced biopharmaceuticals account for less than 15%.

To date, there have only been approximately 30 protein/peptide products enhanced with drug-delivery formulation technologies and subsequently commercialised. Interestingly, the most prevalent use of drug delivery is not with the high-revenue-generating antibodies sector. This group has only two DDS-enhanced products and represents an opportunity for future DDS reformulation. Wyeth's Mylotarg® (gemtuzumab ozogamicin) uses novel antibody–drug conjugation technology to target calicheamicin to the CD33 antigen

for the treatment of first-relapse patients with CD33+ acute myeloid leukaemia. More recently, UCB combined a monoclonal antibody with Nektar's advanced polyethylene glycol (PEG)-ylation technology and launched Cimzia® (certolizumab pegol) for the treatment of Crohn's disease and rheumatoid arthritis.

The greatest commercial application of biopharmaceutical drug delivery has been with interferons and gonadotropin-releasing hormone (GnRH) agonists/antagonists. Through the use of PEGylation and sustained-release depot/implant technologies, many of these products have been reformulated and launched. As shown in *Table 1*, five biologics have surpassed US\$1 billion in annual worldwide sales and all fall within one of the two aforementioned groups. Combined, these leading seven biologics had sales exceeding US\$10 billion in 2008.

Although a small number of therapeutics are currently driving the DDS-enhanced protein/peptide market, drug delivery continues to be integral in solving delivery issues associated with both new drug candidates and established products. Today, there are hundreds of different drug candidates with molecular weight >1,500 currently in clinical development. This presents a tremendous opportunity for the more than 250 companies with novel drug-delivery platforms applicable to proteins and peptides.

As a result, new DDS–biologic products are gaining regulatory approval each year (see *Table 2*). Some approvals, such as that for the histrelin implant from Indevus, are simply for reformulations of previously approved GnRH agonists or interferon. Conversely, some drug-delivery-enhanced biotherapeutics are actually approved as new biological entities (NBEs).

Unfortunately, not all novel DDS protein/peptide formulations prove to be economically viable over time. For example, Nutropin Depot® (somatropin – human growth hormone [hGH]) was approved by the US Food and Drug Administration (FDA) in 1999 as a treatment for growth hormone deficiency in paediatric patients. This therapeutic was a long-acting form of Genentech's hGH using Alkermes' ProLease® injectable extended-release DDS. However, in June 2004, Genentech and Alkermes discontinued Nutropin Depot in the US. The decision was based on the significant resources required by both companies to continue manufacturing and commercialising the product.<sup>4</sup>

Also over a decade ago, ALZA utilised its DUROS® implant technology to develop Viadur™ (leuprolide) for Crescendo Pharmaceuticals. Viadur was the first product to provide continuous, 12-month testosterone suppression with a single treatment. Commercial partner Bayer started sales of Viadur in March 2001 to manage the symptoms associated with advanced prostate cancer (including pain and urinary problems). However, in December 2007 Viadur was discontinued based on diminished market demand and growing manufacturing costs. Bayer concluded that Viadur had limited long-term market viability and its withdrawal from the market was not the result of safety or efficacy issues.

These are just two examples of DDS-enhanced biopharmaceuticals that fell victim to high manufacturing costs and limited sales potential. The next section will discuss additional marketing challenges that face the biotech industry and the reasons why drug delivery must be carefully implemented if it is to be successful.

### Life-cycle Management and Marketing Challenges

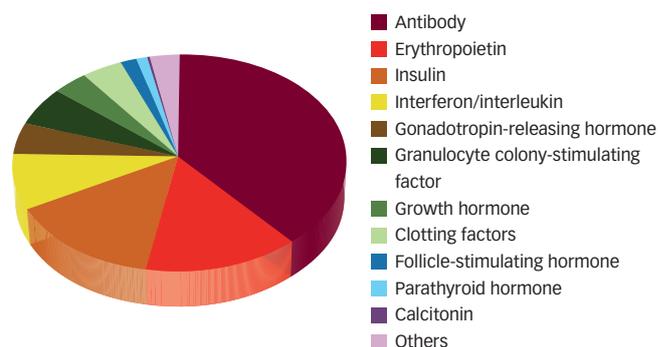
Cost of goods, product competition and time to market are important factors in pharmaceutical life-cycle management. However, on a more basic level there is often a triangular struggle among patients, physicians and the payers that also must be considered and addressed. Balancing these three groups can prove challenging for drug-delivery implementation and reformulation of small-molecule and protein/peptide therapeutics alike.

In an ideal world, medication would be orally administered with limited side effects (for patients), be uncomplicated with high adherence rates (for physicians) and inexpensive (for insurers or other payers). Regrettably, this is just not feasible for most protein and peptide therapeutics. Instead, pharmaceutical/biotech companies and drug-delivery contractors are working together to develop new drug formulations and/or routes of administration to maximise patient benefit and effectively treat disease.

Patients tend to prefer oral dosage forms to injections. In one study to determine the preference of patients for the administration of endocrine treatments, 63% of women with breast cancer preferred daily tablets, 24.5% preferred a monthly injection and 12.5% had no preference.<sup>5</sup> The most cited reasons for tablet preference were convenience and dislike of needles.

Unfortunately, almost all biopharmaceuticals require parenteral administration. While this does present an opportunity for advanced drug delivery (and many universities and companies are pursuing this avenue), oral protein and peptide delivery is not on the horizon.

**Figure 1: Breakdown of Biopharmaceutical Drug Sales Based on 2007 Revenue**



Source: Technology Catalysts International.

**Table 1: Leading Drug-delivery-system-enhanced Protein and Peptide Therapeutics**

Therapeutic (Technology)	2007 Sales (US\$ millions)	2008 Sales (US\$ millions)
Neulasta (PEG)	3,000	3,318
Pegasys (PEG)	1,513	1,512
Leuplin (depot)	1,267	1,289
Zoladex (implant)	1,104	1,138
Sandostatin LAR (depot)	1,027	1,123
PEG-Intron (PEG)	911	914
Lupron Depot (depot)	645	833

PEG = polyethylene glycol. Source: Technology Catalysts International.

**Table 2: Examples of Drug-delivery-enhanced Biopharmaceuticals Approved in the US, 2007–2008**

Brand Name	Drug	Formulation	Company
Supprelin-LA	Histrelin	1-year implant	Indevus
Somatuline Depot	Lantreotide	1-month depot	Tercica
Mircera	Methoxy-PEG epoetin beta	PEGylation	Roche
Cimzia	Certolizumab pegol	PEGylation	UCB
Degarelix	Degarelix	1-month depot	Ferring

PEG = polyethylene glycol. Source: Drugs@FDA.

However, the majority of patients would also prefer less frequent drug regimens for both enteral and parenteral therapeutics. In addition, they want treatments with high quality-of-life outcomes (e.g. fewer side effects and less time away from home). These are two areas that can be more easily addressed by drug delivery and will be discussed in more detail in the next section.

To further stress the need for improved adherence, it has been shown that nearly 75% of patients do not take their medicines as prescribed.<sup>6</sup> Adherence is inversely proportional to the number of times a patient must take his or her medicine each day. The average adherence rate for treatments taken only once-daily is nearly 80%, compared with about 50% for treatments that must be taken four times a day.<sup>7</sup> Medication non-adherence has been associated with an increase in physician visits, higher hospitalisation rates and longer hospital stays. Physicians and insurance payers in the US would therefore prefer treatments with high adherence rates, which often come in the form of sustained release injections via the use of drug delivery.

Unfortunately, advanced delivery systems often have higher costs associated with them. Insurance companies are less likely to reimburse for novel formulations if a less expensive variation exists. As patients prefer treatments covered by health insurance, DDS-enhanced formulations are not always a reimbursed option. Thus, doctor–patient–insurer harmony needs to be considered and optimised for drug-delivery biopharmaceuticals to be successful. If properly balanced, a biologic can be improved with drug-delivery technology and be commercially successful (see *Table 2* for examples of such products). If not, however, there is the possibility for commercial failure (as seen with Pfizer and Nektar's Exubera® inhaled insulin).

### Technical Formulation Challenges

In addition to marketing concerns, there are numerous technical challenges surrounding the formulation and development of biotherapeutics. Issues such as stability, solubility, toxicity and half-life must be considered. Fortunately, many DDS technologies exist for proteins and peptides that are difficult to deliver. The following section will discuss a few of these formulation technologies that are available for biotherapeutics. With the extensive pipelines at many pharma/biotech companies, drug-delivery partnership opportunities are extensive.

### Extending Drug Duration of Action

Biologics tend to degrade very quickly and many require frequent dosing. This shortened half-life is often the result of enzymatic degradation or renal clearance. As a result, various formulation techniques have been devised to prevent premature degradation and/or extend therapeutic activity within the body. Over the decades, researchers have taken different polymer systems to create novel depot and implant technologies. Alternatively, the covalent attachment of PEG polymer chains to a drug or therapeutic protein increases its size and thereby prolongs circulatory time by reducing renal clearance. As a result, over a dozen companies are actively developing PEGylation technology for biopharmaceuticals.

Fresenius Kabi has taken a slightly different approach to the use of polymers to extend a drug's half-life. The company has developed HESylation® technology that utilises hydroxyethyl starch (HES) derivatives linked to drug substances in order to modify the drug characteristics. This modification enables the prolongation of the circulation half-life by increasing the stability of the molecule, as well as by reducing renal clearance, resulting in an increased biological activity. As HES is a modified natural polymer, the body's enzymes can metabolise it.

At present, Fresenius is applying its HESylation DDS to biopharmaceuticals to address protein/peptide/antibody drug-delivery issues. The company has established a broad spectrum of methods for HESylating proteins or peptides at several coupling sites. The increase in size by attaching HES polymers results in lower glomerular filtration rates and, therefore, in a longer half-life. To date, Fresenius Kabi has successfully tested the HESylation technology with EPO, granulocyte colony-stimulating factor (G-CSF) and interferon alpha in animal models.

Another solution to extend a biopharmaceutical's half-life was developed at Syntonix Pharmaceuticals and involves the use of novel Fc fusion technology. Biogen Idec acquired Syntonix in 2007, forming the Biogen Idec Haemophilia Business. The use of Fc-fusion drugs

consists of two copies of a biopharmaceutical linked to the Fc region of an antibody to improve pharmacokinetics, solubility and production efficiency. While Fc fusion technology has been used for many years in approved products (e.g. Enbrel™, Amevive®, Orencia®), the Syntonix proprietary monomeric Fc fusion technology has the potential to deliver enhanced pharmacodynamic properties when applied to recombinant coagulation factors. Fc binds to the neonatal Fc receptor (FcRn) in endothelial cells that line the blood vessels. The fusion molecule, on binding, is protected from degradation and re-released into the circulation. Therefore, this natural pathway for protecting antibodies against destruction also increases the systemic half-life of biopharmaceuticals.

In partnership with Biovitrum AB, Biogen Idec Haemophilia is developing a long-acting rFactor IX (recombinant clotting factor). A phase I/IIa safety and pharmacokinetic study is ongoing in men previously treated with haemophilia B.

### Drug Targeting and Toxicity

Biological drugs often have high toxicity issues that can be addressed through drug delivery. In addition to increasing drug circulation times, PEGylation can mask a biotherapeutic from the host's immune system to reduce immunogenicity and antigenicity. However, an alternative solution to reduce toxicity involves specifically targeting the biotherapeutic to a desired disease site or region of the body. This can be achieved through various means including antibody–drug conjugation, liposomal carriers coated with receptor-targeting materials or the use of external ultrasound.

While applicable to improved pharmacokinetics and drug stability, the use of fusion proteins can also tackle a separate challenge for biopharmaceuticals – therapeutic targeting and transport across biological barriers such as the blood–brain barrier (BBB). Genetically engineering a novel fusion protein to link a biotherapeutic (recombinant protein, monoclonal antibody or small interfering RNA [siRNA]) with a 'molecular Trojan horse' (MTH) can facilitate BBB transport. Scientists at ArmaGen Technologies have developed proprietary MTHs that cross the primate and human BBB faster than neuro-active small molecules such as morphine.

ArmaGen's lead therapeutic is a genetically engineered fusion protein of a neurotrophin and an engineered monoclonal antibody. The antibody crosses the human BBB and acts as an MTH to carry to the brain the attached neuroprotective neurotrophin. A first-in-man phase I clinical trial of the immunoglobulin G (IgG)–neurotrophin is scheduled to begin following completion of a cyclic guanosine monophosphate (cGMP) manufacturing facility. This clinical trial will test the safety and pharmacokinetics of the first IgG–neurotrophin fusion protein to enter human clinical trials.

### Burst Effect

Lastly, DDS technology is being incorporated into parenteral formulations to achieve zero-order kinetics without burst release. Research groups around the world have used different copolymers including poly(lactide-co-glycolide) (PLGA) to create microspheres that strictly control the initial release of peptides. For example, a team from St Marianna University (Kanagawa, Japan) have suggested that initial insulin burst effects can be reduced with PLGA for patients with type 1 diabetes who need construction of a basal insulin profile.<sup>8</sup>

Burst release can also be controlled with PolyActive®, a series of polyether ester multiblock copolymers based on PEG and polybutylene terephthalate (PBT). Developed by OctoPlus in the Netherlands, this system has the ability to vary and control the polymer matrix characteristics, such as the rate of controlled release, degradation, swelling and strength. The use of PolyActive allows for the development of burst-free drug-delivery systems and its hydrophilic nature conserves the stability of labile biopharmaceuticals, such as proteins.

OctoPlus is currently developing a hepatitis C product, Locteron®, based on PolyActive drug-delivery technology. Locteron combines PolyActive with OctoPlus licensee Biolex Therapeutics' BLX-883, a recombinant interferon-alpha produced in its proprietary LEX System™. Biolex completed patient enrolment in a phase IIb clinical study during June 2009.

Thus, biotherapeutics present unique formulation challenges to the industry that include overcoming solubility, toxicity, targeting and stability issues. When balanced with potential marketing and life-cycle management challenges, one can see why there have been a limited number of successful reformulated protein and peptide drugs.

Nevertheless, it has also been shown that drug delivery has an important role in shaping the future biopharmaceutical market. With the emergence of biosimilars in Europe (and eventually the US), the need for DDS is even more critical for future branded products. There exists an enormous opportunity for both the reformulation of currently launched biopharmaceuticals and the application of novel technology to improve NBEs in the biotech pipelines. ■



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