Innovations in Drug Delivery

Broad-based Proprietary Technology Platforms to Address Delivery Efficiency and Improve Patient Compliance

GBI Research
Global Business Intelligence
GBI Research Report Guidance

The report will examine drug delivery technologies under investigation in the next generation of products in key therapeutic areas. Each chapter will highlight emerging companies with technologies that have the potential to transform drug delivery in that specific therapeutic area. The therapeutic areas covered are:

- Chapter three: Oncology
- Chapter four: Vaccines
- Chapter five: Diabetes
- Chapter six: Rheumatology
- Chapter seven: Respiratory diseases
- Chapter eight: Outlook
Executive Summary

Drug delivery technologies provide commercial opportunities for pharmaceutical companies by improving the chances of success for a drug development project. They enable the formulation of a promising molecule that might have poor solubility or require selective delivery to a particular tissue, such as the brain. Similarly, drug delivery technologies may enable companies to differentiate products within crowded therapeutic areas, facilitate life cycle management for existing drugs, and reposition existing drugs—proprietary or generic—in new indications where the needs of the patient population are different or, again, where more targeted delivery is required. Products that are reformulated with novel drug delivery systems do not meet the traditional criteria for innovative products—in other words, products that include new active moieties. Nevertheless, the commercial success of existing products that rely on innovative drug delivery technologies is clear, and these products make significant positive changes for patients. This report provides an overview of the most exciting innovations in drug delivery technologies in major therapeutic areas.

Drug Delivery Requirements Vary Across Therapeutic Areas

Drug delivery requirements vary across therapeutic areas. In oncology, drug delivery companies are focusing on finding new ways to deliver existing molecules, both small (paclitaxel, docetaxel, cisplatin, doxorubicin) and large (Herceptin; Roche), to improve aspects of delivery and provide patient benefit. Reducing drug toxicity is a major driver for this work, and can be achieved by reformulating products to remove toxic excipients or by targeting drugs to cancer cells in order to reduce peripheral toxicity.

<p>| Innovation in Drug Delivery, Drug Delivery Requirements in Different Therapeutic Areas, 2012 |
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<thead>
<tr>
<th>Therapeutic Area</th>
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<th>Reduced toxicity</th>
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<th>Ease of use</th>
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Drug delivery technologies in the field of vaccines are largely being investigated in two distinct contexts. Firstly, companies are aiming to deliver DNA vaccines that have the potential to be more effective than existing alternatives, and to enable product development against more complex targets. These targets include complex infectious diseases for which prophylactic vaccines are not yet available, as well as therapeutic vaccines against cancer and other diseases. Secondly, specialists are investigating the delivery of vaccines to mucosal systems and skin. These routes offer the potential for improved efficacy, and are less invasive.

New routes of delivery are also the focus of efforts in diabetes. The delivery of insulin via routes other than injection has been a long-held aspiration. Multiple companies have tried, and failed, to make this a reality. This report discusses the recent improvements in pen injectors and insulin pumps, which are among the reasons why patients are less likely to object to taking insulin subcutaneously. A second area of interest in diabetes is the development glucagon-like peptide-1 analogs. These are injectable drugs that have seen considerable commercial success since their launch in 2005, and for which there remains scope to reduce the frequency of dosing required.
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2 Drug Delivery - An Overview

2.1 Introduction

Drug delivery refers to the way in which a drug is formulated to achieve a therapeutic effect. Drugs are administered by different routes, most commonly by mouth or directly into the systemic circulation. Other non-invasive routes include topical delivery, transmucosal delivery (ocular, nasal, buccal [cheek], sublingual [under the tongue], vaginal, rectal), or by inhalation (Figure 1). Protein and peptide drugs are among those most commonly delivered intravenously, as they are susceptible to degradation in the digestive tract.

Figure 1: Innovation in Drug Delivery, Commonly Used Options for Drug Delivery, 2012

Source: GBI Research
3 Oncology

3.1 Introduction

Cancer is one of the major causes of death in the developed world; more than XX Americans are expected to die from cancer in 2012 alone. Whilst the number of options to treat the range of cancers has grown over the past two decades, there remains a need for more effective and less toxic treatment options. Indeed, products to treat or cure cancer and improve the quality of life for these patients represent the most active area of pharmaceutical research; more than 980 medicines are in development by US-based biopharmaceutical companies alone (PhRMA, 2012).

Figure 4: Innovation in Drug Delivery, Reducing Drug Toxicity Through Drug Delivery, 2012

- Remove toxic excipients
- Improve bio-availability or solubility and reduce the dose administered
- Delivery to target issue - to preserve integrity of tissue surrounding a tumor
- Avoid systemic side effects
- Avoid drug resistance
- Reduce infusion time

Source: GBI Research
3.3 Protein-Based Drug Delivery Systems

3.3.1 Albumin

Albumin, a plasma protein that naturally carries endogenous hydrophobic molecules such as vitamins, hormones, and other water-insoluble substances found in plasma, has been investigated as a drug delivery system for a number of years. Albumin has an important role in the transfer of protein bound and unbound plasma constituents across endothelial membranes through a caveola (a small invagination of plasma membrane) that transports the albumin-drug complex into the extracellular space. A second mechanism with Secreted Protein, Acidic and Rich in Cysteine (referred to as SPARC), thought to be selectively secreted by tumors, is involved in binding to the albumin-drug complex and releasing the drug close to tumor cells (Kratz, 2008).

Thus, despite the promise of the delivery method, the extent to which Abraxane represents an improvement over paclitaxel in efficacy is not yet entirely clear. Reviewing the data suggests differences in the safety profiles of the two agents that, in addition to the improved dosing convenience, may make Abraxane a more acceptable treatment for patients. Celgene acquired Abraxis BioScience for approximately $XX billion in 2010. Abraxane sales were less than $XXm in 2011.

A number of other drugs that use albumin as a delivery system are currently being developed (Table 5). These include:

- CytRx Corporation’s INNO-206: Doxorubicin modified through attachment of an acid sensitive linker [(6-maleimido)caproylhydrazone; EMCH]. The EMCH group forms a covalent link with endogenous circulating albumin once the drug has been administered, which is cleaved when the albumin enters the acidic environment of the tumor to release doxorubicin. INNO-206 entered clinical development in 2006 and is currently being investigated in a Phase IIb clinical trial in comparison with native doxorubicin. The study will measure progression-free survival, tumor response and overall survival of patients with advanced soft tissue sarcomas.

- Celgene carried out initial clinical studies with nab-docetaxel (ABI-XX), nab-rapamycin (ABI-XX) and a nab-paclitaxel/nab-tanespimycin (ABI-010) combination, although none of these drugs appears in the company’s current therapeutic pipeline.

- Novozymes Biopharma is a leader in the field of albumin fusion technology. The company has developed a number of options for covalent linkage of albumin to peptides and proteins, and has licensed its technology to Human Genome Sciences Inc, Teva, CSL Schering and Dyax. HGS partnered one of its products (Zalbin; albumin-interferon alfa) with Novartis for the treatment of hepatitis C. Development of this product ceased after the companies received a Complete Response Letter from the FDA in October 2010. Issues had arisen concerning the benefit:risk ratio of the product. Other products licensed by Novozymes will be discussed in Chapter Six.
9 Appendix

9.1 Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AAV</td>
<td>Adeno-Associated Virus</td>
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<tr>
<td>ADC</td>
<td>Antibody-Drug Conjugates</td>
</tr>
<tr>
<td>BLP</td>
<td>Bacterium-Like Particle</td>
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<tr>
<td>CFC</td>
<td>Chlorofluorocarbon</td>
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<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
</tr>
<tr>
<td>DPI</td>
<td>Dry Powder Inhaler</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EMCH</td>
<td>(6-maleimido)caproylhydrazone</td>
</tr>
<tr>
<td>ETEC</td>
<td>EnteroToxigenic <em>E. coli</em></td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GIPET</td>
<td>Gastrointestinal Permeation Technology</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Glucagon-like peptide-1</td>
</tr>
<tr>
<td>GRAS</td>
<td>Generally Recognized as Safe</td>
</tr>
<tr>
<td>HAI</td>
<td>Hemagglutination Inhibition</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>IU</td>
<td>International Units</td>
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<tr>
<td>mRNA</td>
<td>Messenger Ribonucleic Acid</td>
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<tr>
<td>MTS</td>
<td>Microstructured Transdermal System</td>
</tr>
<tr>
<td>MVA</td>
<td>Modified Vaccinia Virus Ankara</td>
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<tr>
<td>LT</td>
<td><em>E. coli</em> Heat-Labile Enterotoxin</td>
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<tr>
<td>LTRA</td>
<td>Leukotriene-Receptor Antagonist</td>
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<tr>
<td>PEG</td>
<td>Polyethylene Glycol</td>
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<tr>
<td>PFS</td>
<td>Progression-Free Survival</td>
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<tr>
<td>PLA</td>
<td>Poly(Lactic Acid)</td>
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<tr>
<td>PLGA</td>
<td>Poly(Lactic co-Glycolic Acid)</td>
</tr>
<tr>
<td>pMDI</td>
<td>Pressurized Metered Dose Inhaler</td>
</tr>
<tr>
<td>PSMA</td>
<td>Prostate-Specific Membrane Antigen</td>
</tr>
<tr>
<td>PRINT</td>
<td>Particle Replication In Non-Wetting Templates</td>
</tr>
<tr>
<td>RSV</td>
<td>Respiratory Syncytial Virus</td>
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<tr>
<td>TD</td>
<td>Traveler’s Diarrhea</td>
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<td>TNFα</td>
<td>Tumor Necrosis Factor-alpha</td>
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<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
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9.2 References


9.3 Methodology

GBI Research’s dedicated research and analysis teams consist of experienced professionals with a pedigree in marketing, market research, consulting backgrounds in the medical devices industry and advanced statistical expertise.

GBI Research adheres to the Codes of Practice of the Market Research Society (www.mrs.org.uk) and the Strategic and Competitive Intelligence Professionals (www.scip.org).

All GBI Research databases are continuously updated and revised. The following research methodology is followed for all databases and reports.

9.3.1 Primary Research

GBI Research conducts hundreds of primary interviews a year with industry participants and commentators in order to validate its data and analysis. A typical research interview fulfils the following functions:

• It provides first-hand information on the market trends, growth trends, competitive landscape, future outlook etc;
• Helps in validating and strengthening the secondary research findings; and
• Further develops the analysis team’s expertise and market understanding.

Primary research involves e-mail correspondence and telephone interviews for different topics covered in the report. Those who took part in interviews for this report include:

Eslie Dennis, Executive Director of the Predictive Safety Testing Consortium and Polycystic Kidney Disease Consortium, The Critical Path Institute
Ton Rijnders, Scientific Director, Top Institute (TI) Pharma
Bryn Williams-Jones, Founder and Chief Operating Officer, Connected Discovery Ltd

9.3.2 Secondary Research

Secondary research was carried out on internal and external sources to source qualitative and quantitative information in the report.

The secondary research sources that are referred in this report include, but are not limited to:

Company websites, annual reports, financial reports, investor presentations and SEC Filings;
Industry trade journals, scientific journals and other technical literature;
Relevant patent and regulatory databases;
National government documents, statistical databases and market reports; and
News articles, press releases and web-casts specific to the companies operating in the market.
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