

# Executive Summary

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The roll call of therapeutic proteins includes some of biotechnology's most celebrated successes: clotting factors, anticoagulants, modern insulins, growth hormone, follicle-stimulating hormone, hematopoietic growth factors, interferons, and interleukins. The combined sales of therapeutic proteins—\$34 billion in 2004 and projected to grow to \$52.2 billion in 2010<sup>1</sup>—is testimony to their value in treating a wide range of serious diseases.

As patents on honored and famous proteins wind down, their owners naturally seek to protect their markets against interlopers. And in battles for market share going on today and battles to come, protein delivery technologies—the subject of this report—are major weapons of offense and defense. For if a therapeutic protein is bringing in big money and its patent is on the wane, someone somewhere with a clever technology is planning a market invasion based on improving how the protein is delivered. Protein delivery technologies are going to intensify competition in many markets. Thus, our report includes discussions of protein delivery technologies developed by:

- 19 companies targeting improved insulin delivery
- 5 companies targeting improved erythropoietin delivery
- 8 companies targeting improved interferon delivery
- 6 companies targeting improved growth hormone delivery
- 7 companies targeting improved parathyroid hormone delivery

For some proteins and peptides, improving delivery may be essential in order to explore new indications. Here, protein delivery technologies can be tools for market expansion.

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1. Pavlou AK and Reichert JM. Recombinant Protein Therapeutics—Success Rates, Market Trends and Values to 2010. *Nat Biotech.* 2004;22:1513-1519.

Our report focuses on 2 trends in therapeutic protein delivery technology, both of which have seen some success in producing FDA-approved products.

***Trend #1: More protein engineering technologies are available than ever before to improve protein delivery characteristics***

Without question, the most desired improvement, the one for which market rewards are greatest, is longer protein half-life in serum. Which is why technological development in this area is so competitive. Chapter 2 discusses 13 approaches to extending therapeutic protein half-life.

When a therapeutic protein has a short half-life, physicians may inject very high doses to delay as long as possible when protein concentrations fall below therapeutic levels. Unfortunately, high initial peak levels of therapeutic proteins sometimes cause side effects. By extending therapeutic protein half-life, lower doses can maintain effective therapeutic action longer, and high, potentially toxic doses become unnecessary. The risk of adverse events abates. Dosage schedules become more convenient for patients and physicians alike. Thus it is no surprise that in the hepatitis C market, for example, extended half-life interferon- $\alpha$  analogs injected once a week have supplanted the original interferon- $\alpha$  (injected thrice weekly). Some half-life extension technologies may also reduce protein manufacturing costs, increase batch-to-batch consistency, and enable limited manufacturing capacity to be used more efficiently.

For years, the only successful technology for extending protein half-life was PEGylation. The FDA has approved 6 PEGylated therapeutic proteins. Now, 2 other half-life extension technologies have received FDA approval: hyperglycosylation was used to create Amgen's erythropoietin analog, Aranesp; serum albumin-binding fatty acids were used to create Novo Nordisk's long-acting basal insulin, Levemir. Although PEGylation technology continues to advance and become more versatile, it is no longer the only game in town.

Additionally, other technologies are being used to reduce therapeutic protein immunogenicity and aggregation. This is the subject of Chapter 3.

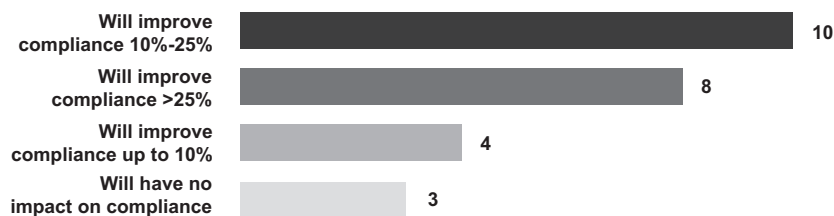
***Trend #2: Noninjection technologies are beginning to deliver therapeutic proteins without needles***

Transdermal, oral, pulmonary, and nasal delivery technologies are well established for small molecules. For therapeutic proteins, until recently they failed almost completely. The challenge for delivering proteins is to raise bioavailability from abysmal levels to at least 10%, and preferably much higher. Noninjection delivery technologies must also avoid pain and irritation and usually achieve rates of onset comparable to those with subcutaneous injections.

Chapters 4-6 discuss:

- 6 technologies for transdermal protein delivery
- 5 technologies for oral protein delivery
- 6 technologies for pulmonary protein delivery
- 3 technologies for nasal protein delivery

No one likes needles. We submit to them, though, because for some drugs there are no delivery alternatives. This is especially true for proteins. Almost every therapeutic protein is administered by intravenous, subcutaneous, or intramuscular injection. When frequent injections are required for treating chronic diseases, however, dislike of needles becomes a serious matter. For example, among diabetics it is documented that fear of needles causes many to delay insulin injections for years, at the risk of blindness, amputation and death. Better ways to deliver insulin are needed, and other therapeutic proteins as well. It is widely expected that noninjection protein delivery technologies will improve compliance and reduce complications arising from compliance failure. Because noninjection protein delivery is a young field, however, predictions diverge on how much compliance will improve. This can be seen in the figure below, which is part of a survey included with this report. Noninjection technologies must advance further before their effects on compliance are known.

**Figure. Survey Results: How will noninjection delivery vehicles affect patient compliance with protein therapy?**

n=25

Source: CHI Advances Reports, Protein Drug Delivery Survey, December 2006

The most exciting news in noninjection protein delivery is the FDA approval in 2006 of Exubera, a dry powder aerosol technology for inhaled delivery of insulin. Exubera is a triumph, finally removing doubts that therapeutic proteins can be delivered by means other than injection. Now the question is, which other noninjection delivery routes will also work? Clinical trials should provide some answers within the next few years.

Exubera is so new that a number of important questions cannot yet be answered. One is the long-term safety of inhaling insulin. This, of course, will be closely watched. Another is how much Exubera will increase compliance to insulin therapy. Another regards the versatility of Exubera technology. Insulin is a rather small protein, around 5.8 kilodaltons. Can dry powder aerosol technology efficiently deliver much larger proteins? Answers await further investigations. In the meantime, we disagree with blanket dismissals that no noninjection technology can deliver larger proteins up to the size of antibodies (around 150 kilodaltons). We note, for instance, that one oral and pulmonary protein delivery technology described in this report is based upon a natural antibody transport mechanism and that the company behind this technology was recently acquired by one of the leading biotechnology companies. In our view, we would do well to avoid preconceptions and await the clinical data.

One thing these technologies will not do is banish injections altogether. Especially in hospital settings and for acute therapies, we expect therapeutic proteins will continue to be injected for years to come. That said, as more protein delivery technologies gain regulatory approval, we predict that patient and physician expectations will gradually change. If insulin can be delivered with an inhaler, why not other proteins, they may ask. This in turn will influence more companies developing therapeutic proteins to seriously consider noninjection delivery.

### **Will these Trends Merge?**

Will therapeutic proteins with longer half-lives and other improvements eventually be delivered without injection? We believe that some will, once more of these technologies achieve regulatory approval. A few companies already participate in both technological trends and are in position to take early leads in this direction. Beyond this observation, many companies working on half-life extension may be only partially familiar with the capabilities of noninjection technology companies, and vice versa. Therefore, advantageous trend-merging technology combinations may exist that they are unaware of. Our hope is that the information in this report will help bring new technology partners together to mutual benefit.

### **Scope of this Report**

Technologies discussed in this report are those most likely to affect the delivery of therapeutic proteins within the next 5 years. They are being tested today in clinical trials, or will be within a few years. They are not embryonic technologies under development in academic laboratories.

Technologies to enhance enzyme specific activity or improve binding affinity for receptors are not covered. These aspects of therapeutic protein function are not generally considered drug delivery characteristics.

This report also does not cover vaccine delivery, and with one exception does not cover delivery of monoclonal antibodies. Monoclonal antibodies are proteins, of course, but are generally considered a class unto themselves. *Therapeutic proteins* is a term often not intended to include monoclonal antibodies, and we have followed

that convention here. The companies in this technology survey are not working on monoclonal antibody delivery. Regarding protein half-life extension, the main protein engineering subject in this report, monoclonal antibodies have very long half-lives compared to most proteins and are not generally believed to need further half-life enhancement. The exception is monoclonal antibody fragments that have lost the Fc domain. Antibody fragments have short half-lives that can be extended by technologies described herein. As for the non-injection technologies discussed in this report, they are not being developed expressly to deliver monoclonal antibodies, although some might be used for that purpose.