

SPECIAL FEATURE

PROTEINS & PEPTIDES: DEPENDENT ON ADVANCES IN DRUG DELIVERY?

By: Cindy H. Dubin, Contributor

The success of protein and peptide therapeutics is revolutionizing the biotech and pharmaceutical market, spurring the creation of next-generation products with reduced immunogenicity, improved safety, and greater effectiveness, states a new report, *Next Generation Protein Engineering & Drug Design*. New technologies and genetic and chemical techniques will ensure a competitive edge in developing improved protein- and peptide-based therapeutics.


The report points out that the protein engineering market in 2006 was worth almost \$67 billion (10% of total pharma sales) and is forecast to rise to \$118 billion (12% of pharma sales) in 2011.

Despite their remarkable success, protein drugs continue to suffer from drawbacks, especially with respect to their delivery (subcutaneously or intravenously injected). The past 3 years have seen approvals of products for non-parenteral delivery, alongside advances in parenteral protein and peptide drug delivery.

The increased use, development, and discovery of protein therapeutics will lead to increasing opportunities for drug delivery companies. Pharma companies need to use these technologies to gain a competitive edge in an increasingly crowded therapeutic protein market. The protein therapeutic market is largely immediate release, but there is a trend moving toward increased sustained-release formulations.

While the majority of protein therapeutics on the market do not have devices available, this is a growing segment of the market, and Datamonitor expects the growth to accelerate. Datamonitor believes companies should explore the use of devices to maximize the potential of their products and differentiate them from competitors.

Improvements in protein drug delivery will increase patient compliance and expand many drug markets. In addition, some new formulations may be patentable and can therefore extend a drug's life cycle. For these reasons, pharmaceutical and biotechnology



A column for large-scale peptide purification at American Peptide Company, Inc.

companies are researching and testing new delivery methods for protein drugs, according to Market Research.

Companies see the potential for improving the delivery methods for protein- and peptide-based drugs. For some, this means extending peptide half-life or improving manufacturing processes, while others are researching active coatings. Some companies on the cutting edge of protein and peptide drug delivery include American Peptide, SurModics Pharmaceuticals (formerly Brookwood Pharmaceuticals), Emisphere, PolyPeptide, and 3M Drug Delivery Systems.

AMERICAN PEPTIDE: IMPROVING DELIVERY THROUGH SYNERGY

American Peptide Company, Inc. (APC) is a CMO offering Total Peptide Management to clients. The program is a customized service platform, which comprises a set of comprehensive services, including process development; scale-up production; analytical and process validation; stability studies; Chemistry, Manufacturing, and Controls (CMC); Drug Master Files (DMF) and regulatory support. Since the program's launch early last year, APC has seen an increased collaboration between APC and clients in moving projects forward, explains Scott Caton, Director, GMP Quality Control at APC.

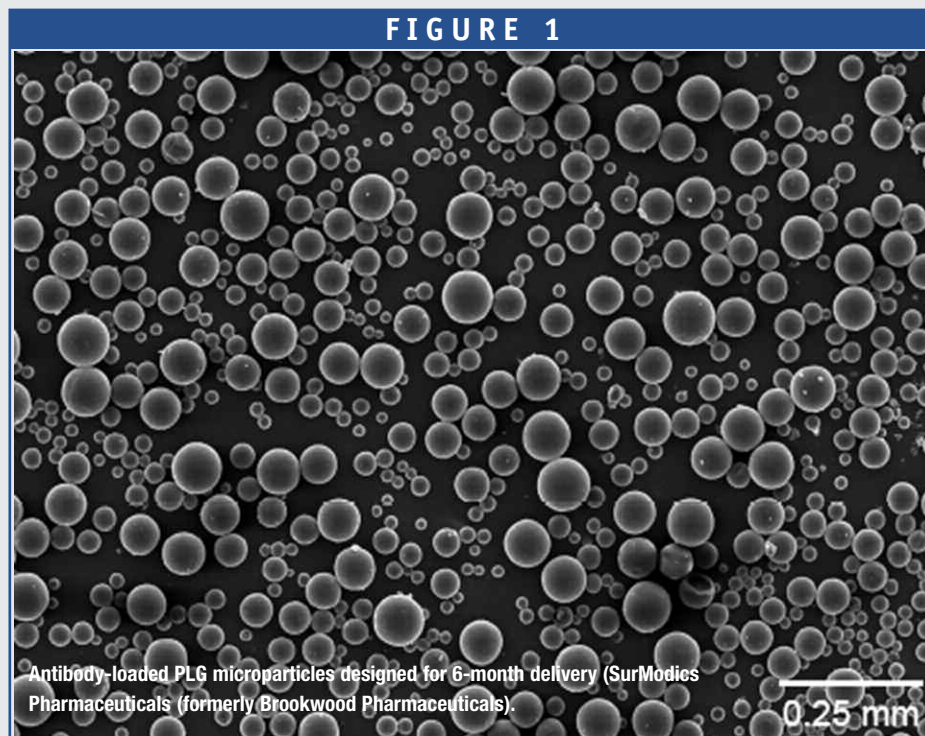
In order to achieve the desired efficacy, peptide drugs need to target the appropriate site and also have a therapeutic half-life. Patricia Haller, PhD, Director, GMP Manufacturing and Process Development at APC, believes these challenges can be overcome by engineering the peptide sequence or by conjugating the peptide to carrier molecules, such as PEG or antibodies.

American Peptide works with clients to supply engineered peptides so they can be screened for pharmacokinetic profiles and efficacy. In addition, APC has expertise in peptide conjugation and other difficult-to-manufacture peptides.

Since the acquisition by Otsuka Chemical Company (OCC) in September 2008, APC and OCC are creating new synergistic opportunities in improving drug delivery that will benefit the pharma and biotech companies.

APC's target clients are pharmaceutical and biotech companies using peptide-based APIs for drug discovery and consumer products development, explains Gary Hu, APC Vice President, Sales and Marketing. Therapeutic focus areas are in cancer vaccines, neurodegenerative diseases, and metabolic disorders. American Peptide has developed proprietary technologies that allow the company to quickly develop economically viable, environmentally sound, scalable manufacturing processes for peptide-based APIs.

"Our expertise in both solid- and



solution-phase synthesis methodologies, as well as hybrids, allows us to let a specific target dictate the most appropriate synthetic methodology. This ground-up process mapping allows us to accommodate a host of unnatural functionalities commonly found in state-of-the-art peptide therapeutics, ranging from small molecule conjugates to polymer modifications," says Firuz Shakoori, Director of Sales at APC.

"As we are in the midst of a global economic downturn, the future of the peptide industry in the coming years is far from certain," Mr. Shakoori continues. "The API business is very dependent on research, development, and outside sourcing from Big Pharma, biotech, and academia. This situation notwithstanding, American Peptide will remain in an upbeat mode with current and future expansions and bring new technologies to enable the synthesis of a wide-range of peptide-based compounds. This is particularly important as the next generation of peptide therapeutics will be increasingly complex, far beyond naturally occurring peptide hormones, and will be critical to retain our competitive place in US-based manufacturing. We anticipate that with our expanded infrastructure and highly skilled technical staff, APC will be well-poised to partner with Big Pharma and biotech companies for the next 5 to 10 years."

SURMODICS PHARMACEUTICALS: NEW-GENERATION ANTIBODIES

SurModics Pharmaceuticals (formerly Brookwood Pharmaceuticals) is developing injectable microparticle products for 4- to 6-month delivery of proteins. Most recent activities have been directed toward the delivery of new-generation, therapeutic antibodies in several therapeutic areas. These microparticles comprise antibody encapsulated within lactide/glycolide (PLG) excipient. Formulating and stabilizing these proteins without denaturation is a challenge that can result in the formation irreversible aggregates, explains Thomas R. Tice, PhD, Vice President of Research, SurModics Pharmaceuticals.

Surmodics' low-shear microencapsulation process technology and formulation compositions can maintain protein integrity. Stability and release kinetics can be improved with proprietary microencapsulation technology involving conjugation of protein to hydrophilic polymers. Further, Surmodics' key strategic investment in construction of a state-of-the-art isolator manufacturing capability allows the production of commercial products aseptically. PLG microparticles offer a long safety record of PLGs as evidenced by the many examples of drug delivery products and medical device products that are on the market, says Dr. Tice.

Quickly commercializing safe and effective products to benefit patients and improve quality of life is the charter of most pharmaceutical and medical device companies. Many drugs, and in particular peptide therapeutics, benefit from controlled delivery systems. While these delivery systems can significantly improve the therapeutic product, peptides are not typically screened or optimized for properties that would allow more effective implementation in controlled delivery systems. In the cases where controlled delivery offers significant

advantages, this inevitably results in delays during formulation development, which could be avoided by simply choosing or designing the drug with controlled delivery in mind, says Dr. Tice.

Design for Peptide DeliverySM is a solution-oriented approach with the SurModics and Genzyme Pharmaceuticals collaboration, which addresses peptide formulation issues early during development by screening lead compounds or assessing drug development candidates for their ability to be effectively implemented in proven drug

delivery systems. Proven drug delivery technologies, having gone through the rigors of safety testing, regulatory review, product approval, and demonstrated market acceptance, are greatly preferred to quickly advance the product to market, explains Dr. Tice. Using the Design for Peptide Delivery strategy, the SurModics/Genzyme team performs drug delivery-based screening on lead peptides in discovery to provide the optimum peptide for use in controlled delivery.

“We see a substantial growth area for the systemic and local delivery of therapeutic antibodies and related macromolecules,” says Dr. Tice.

FIGURE 2

The PolyPeptide Group utilizes solid-phase peptide synthesis (SPPS) for the manufacture of its many custom and generic peptide-based APIs.



EMISPHERE TECHNOLOGIES: NEW FRONTIERS IN DRUG DELIVERY

Emisphere's core business strategy is to use its proprietary Eligen[®] Technology to develop novel oral forms of injectable drugs or poorly absorbed compounds. The broadly applicable Eligen[®] Technology and Emisphere's current product candidates in the pipeline represent the foundation of the company's value proposition and create significant opportunities for growth. Emisphere's pipeline includes product candidates that have reached clinical development as well as a variety of preclinical research and development programs.

Emisphere is currently active in the area of peptide delivery through partnerships with Novartis for the oral delivery of salmon calcitonin and parathyroid hormone, and with Novo Nordisk for delivery of its proprietary GLP-1 analogs.

The Eligen[®] Technology is effective in delivery of biologically active agents with a range of molecular sizes and configurations. The technology is supported by more than 4,000 carriers and 2,000 patents. Eligen[®]-based formulations can be implemented readily with new delivery candidates.

An optimized commercializable formulation based on the existing technology can be typically achieved with a new drug candidate in a matter of several months or less.

Eligen[®] permits absorption of therapeutic

molecules directly through the gastric mucosa.

“It is the only drug absorption technology ready for market that acts in this manner,” says Dr. Gary Riley, Vice President, Nonclinical Development and Applied Biology, Emisphere Technologies. “It allows drugs not otherwise bioavailable by the oral route for reasons of poor permeability to be administered orally. It also provides important advantages of safety and efficacy over other technologies designed to improve oral bioavailability.”

An Eligen® carrier is co-formulated with the molecule of interest to form a reversible drug/carrier complex. After oral administration in tablet form, the complex is transported across the gastric mucosal membrane by the action of the carrier in transiently altering gastric epithelial permeability. The only entities reaching the circulation are drug and carrier. There is no evidence that the complex circulates, and no novel molecules are formed. The carrier is not pharmacologically active. It has no toxicity at the carrier doses used (typically less than 300 mg/dose), and the carrier is rapidly metabolized without accumulation.

Eligen® carriers also protect molecules from degradation in the GIT in the interval before absorption occurs. This is a most important feature where proteins and peptides are concerned, says Dr. Riley.

Several Eligen® formulations are in late development. A vitamin B12 formulation is expected to be marketed in 2010, and the Novartis Eligen®/salmon calcitonin products for osteoporosis and osteoarthritis are currently in late Phase III testing in approximately 6,000 patients. These products are expected to reach the market in approximately 2012.

“Eligen® formulations have the ability to transform the market for poorly absorbed molecules,” says Dr. Riley. “Our products simplify administration procedures for these drugs and do so at a product cost that is less than the aggregate cost of parenteral administration.”

Eligen® acts as a drug molecule chaperone, protecting macromolecules from degradation before absorption occurs. Another benefit is passive transcellular drug uptake. It does not allow uptake of “bystander” molecules in the GIT.

“In contrast, a number of competing technologies use paracellular transport mechanisms based on short chain fatty acids. This approach may allow absorption of non-target molecules and therefore raise potential safety concerns,” says Dr. Riley.

Emisphere markets its Eligen® Technology to companies wishing to market oral dosage forms of drugs having a moderate therapeutic index. This includes molecules as diverse as metal ions, proteins, peptides, and oligonucleotides. As with other drug delivery technologies, the driver for adoption is not a single therapeutic focus but compatibility with the technology. Eligen is compatible with many classes of molecules other than proteins and peptides. Emisphere is continuing to explore and optimize the delivery of a wide class of organic and inorganic molecules.

“The Eligen® model of drug delivery continues to be most attractive and is expected to continue to provide a suitable platform for oral delivery of otherwise poorly absorbed drugs,” says Dr. Riley. “The current surge in development of analogs of macromolecules having properties of increased stability and decreased rates of body clearance renders these classes of molecules increasingly compatible with the Eligen® Technology.”

POLYPEPTIDE LABORATORIES: PEPTIDE MANUFACTURING OF ANY SIZE

PolyPeptide Laboratories manufactures the peptide-based APIs that go into drug delivery devices or formulations. Its customers develop novel delivery methods, which may involve molecular design of the peptide, conjugation of the peptide to other molecules, incorporation into polymeric matrices, formulation composition, the use of devices, etc. PolyPeptide can assist by manufacturing the custom-designed peptide or by coupling the peptide to other non-peptide moieties.

“In the case of peptide-based substances, we see the main challenge to the drug delivery industry being that most peptides cannot be administered orally,” says Dr. Rodney Lax, Senior Director of Business Development, North America, PolyPeptide

Laboratories.

In the few cases where peptides can be dosed orally, it is either because the structure of the peptides prevent enzymatic degradation in the upper gut or that they are administered in massive doses - a strategy that is not economically viable for most peptides. Injection is usually not well suited for self-medication because of poor patient compliance.

There are a number of delivery options apart from the oral and injection route. These include oral, nasal, and buccal administration; a number of devices, such as patches and needle-free injection devices; and externally or internally located administration devices.

PolyPeptide Laboratories provides several strategies for peptide synthesis to support projects of any size. Peptide synthesis is accomplished using either solid phase peptide synthesis (SPPS) or liquid (solution) phase synthesis (LPPS). Hybrid approaches involving fragments manufactured by SPPS and coupled in solution phase are also used. The company is adequately equipped to support both solid-phase and solution-phase projects with material requirements in excess of hundreds of kilograms per year.

A major part of peptide manufacturing is the purification and isolation procedures. PolyPeptide uses some of the largest state-of-the-art equipment in the industry allowing for the manufacture of peptide APIs in single lots of up to about 10 kg, depending on solubility and method of synthesis. For very large manufacturing processes in which lyophilization becomes a bottle-neck for the isolation step, other procedures, such as spray-drying or, when appropriate, precipitation, are being investigated.

The newly enlarged PolyPeptide Group currently supports a large and diverse selection of clients. This includes universities and the full gamut of biotech and pharmaceutical companies.

“We do business with commercial organizations with less than 10 employees to more than 50% of the top 20 Big Pharma companies, says Dr. Lax. “With our comprehensive range of services, we can support customers with catalog material and small-scale custom synthesis for research and

lead development through to GMP campaigns from gram to multi-10 kilogram quantities. We have a range of generic peptide APIs approved in the US, Europe, and elsewhere. Most of our large-scale manufacturing is for the human and veterinary pharmaceutical market.”

Historically, the main uses for peptides have been hormonal lesions and hormone-related disease, but today, they have applications in nearly every medical indication from hormonal/metabolic disorders, such as diabetes and obesity through pain management, bone disease, cancer, infection, imaging, and much more. There are hardly any areas of medicine that do not use or not developing peptide-based APIs.

“We see the peptide industry continuing to grow for well over the next 5 to 10 years,” says Dr. Lax. “The growth over the past few years reflects rekindled interest in peptides due to their specificity and favorable safety profile. The cost of manufacturing has also come down.”

As the human genome continues to be unraveled, the number of new targets continues to increase. Peptide- (and protein)-based drugs are building part of the arsenal of drugs to treat “previously untreatable” disease. As such, there is no alternative therapy, and the pharmaceutical industry is under intense pressure to develop acceptable methods of administration that will ensure patient compliance.

“There is no doubt that delivery of peptide drugs will continue to be an area of research, and PolyPeptide is excited to be working with the industry to bring new peptide therapies to fruition,” says Dr. Lax.

3M: MEETING PROTEIN & PEPTIDE CHALLENGES

3M Drug Delivery Systems has multiple delivery technologies that apply to the delivery of proteins and peptides. 3M’s Microstructured Transdermal System (MTS) uses a molded plastic array to temporarily disrupt the normal skin barrier and allow intradermal delivery of many actives, including proteins and peptides that would not otherwise penetrate through the skin. The

FIGURE 3

3M’s sMTS Array for Systemic Delivery



company is working on multiple variants of the MTS technology to solve different delivery challenges, including solid microstructures coated with active (sMTS), hollow microstructures for fluid delivery (hMTS), and an MTS device in which the microstructures are used as a pretreatment to facilitate subsequent delivery of active through the pretreated skin area.

3M Drug Delivery recently announced a co-development project with Vaxinnate Inc. in which the company is using the MTS technology for delivery of a flu vaccine, and 3M is working on several other protein delivery projects using both the solid and hollow versions of the MTS technology.

3M also offers inhalation drug delivery systems for delivery of proteins and peptides to the lungs. Most recently, 3M has added a range of dry powder inhalation (DPI) devices and technologies that offer another solution for pulmonary delivery of proteins and peptides, particularly those with dosing requirements in the 1- to 20-milligram range. A range of device formats are available, including a single-dose disposable device that is well suited to delivery of expensive protein and peptide APIs.

“There are the usual challenges inherent in protein/peptide formulation development, such as maintaining physicochemical stability as well as the biological activity of the API throughout the product shelf-life, and ensuring efficient utilization of the often costly protein or peptide API throughout both the manufacturing and the delivery process,” says Tim Peterson. “We are also addressing the challenge of developing MTS products with a degree of sterility assurance that goes

well beyond that of traditional transdermal products, and is often complicated by the incompatibility of proteins with radiation sterilization.”

The sMTS system may help address the stability concerns through its solid-state coating, which for some protein and peptide APIs, offers stability advantages over typical parenteral formulations. For some of these APIs, it may be possible to reduce the cold chain storage requirements, providing substantial advantage in the distribution of these medicines globally, but especially to the developing world.

With regard to the efficiency of API utilization, 3M has demonstrated that both the sMTS and hMTS technologies are highly efficient, providing bioavailability that is very similar to subcutaneous injection with a range of peptides and proteins from 1,000 to 150,000 MW. For vaccine delivery, the sMTS technology has been tested with a range of antigens, and in some cases, has been shown to provide an equivalent immune response to IM injection with up to a 10-fold reduction in dose. This dose-sparing capability of sMTS may be further enhanced when the vaccine is co-administered with 3M’s toll-like receptor agonist vaccine adjuvants, allowing for up to a 64-fold reduction in dose compared to IM administration.

A key advantage of 3M’s solid MTS microneedle system is the ability to deliver a range of biopharmaceuticals and vaccines, systemically or intradermally. For pharmaceutical companies, sMTS fits well with systemic delivery of potent small molecules salts and proteins: it provides

bioavailability comparable to SC injection and the potential to extend product life in more mature market segments. In addition, sMTS enhances the efficacy of vaccines by targeting the antigen to key antigen-presenting cells within the skin, thereby improving delivery efficiency and reducing dose requirements.

In addition, for 3M's sMTS systems, microstructures won't fracture or break, eliminating risk of in situ fragmentation. For patients, sMTS provides a simple-to-use, self-administration application with minimal pain.

"We have made a number of recent advances in our sMTS technology," says Mr. Peterson. "Our formulation and coating technology has progressed to the point where we are achieving very precise and reproducible coatings on the microstructures."

In many cases, these coatings release >90% of the protein or peptide API after less than 5 minutes of wear time. 3M has also leveraged the microreplication and

micromolding expertise to improve its MTS arrays, optimizing the depth of penetration into the skin while simultaneously simplifying the applicator systems required for placement of the arrays.

"We are excited about the potential of our hMTS technology," says Mr. Peterson. "This system consists of a wearable hollow microneedle array coupled to a liquid reservoir for intradermal infusion of liquid formulations. In the past year, we have conducted a clinical study in which the hMTS device was used to rapidly deliver high volume infusions (up to 1 ml) with barely perceptible sensation to the subjects. We have also conducted animal studies with a range of peptide and protein APIs, including a polyclonal antibody fraction, demonstrating a similar pharmacokinetic profile to subcutaneous injection. This technology provides an easy-to-use and virtually painless alternative for many protein or peptide formulations currently given by injection."

He adds that the development of protein

and peptide drugs will continue to accelerate in the coming years, providing increasing opportunities for alternative delivery systems with a compelling value proposition.

"Some of the first-generation injectable products will likely also be developed in alternative delivery systems as a means to provide product differentiation and stay ahead of biosimilars or other competitive products," says Mr. Peterson. "At 3M, with our sMTS and hMTS platforms, along with our inhalation technologies, we believe we offer a range of cost-effective and differentiated solutions to meet the current and future challenges of protein and peptide delivery." ♦