Market Growing for Custom-Made Peptides — — Expansion Attributed to Increase Use in Drug and Vaccine Development

Continued growth and a changing landscape characterize the custom peptides marketplace, as suppliers ramp up capacity to meet rising demand in both the research and therapeutics markets. With pharma increasingly focusing on biologics and moving peptide drugs through their pipelines into late-stage development, and the research community focusing significant resources on vaccines and biomarker discovery, the demand for higher quality proteins and peptides, large peptide libraries for screening applications, and modified GMP peptides with improved stability profiles and pharmacokinetic properties is driving double-digit annual growth.

Even as strong demand shows no signs of abating, at least in the near term, building pressures to drive down costs, assure higher quality-control standards, and increase the throughput and efficiency of synthesis processes will continue to drive development of novel synthesis, modification, and purification strategies, encourage companies to target emerging markets, and expand globally to maintain a competitive advantage.

Trends to watch include rapid growth in the areas of vaccines, biomarkers, and protein therapeutics, the growing popularity of microwave-based peptide synthesis technology, and innovative strategies to enhance delivery and bioavailability of peptide drugs, as well as increasing investment in China and the emergence of Chinese companies competing for global market share for custom peptides and raw materials.

Making headlines, **Lonza** (www.lonza.com) acquired Brussels-based peptide manufacturer **UCB Bioproducts** (www.ucb-bioproducts.com)in late February for E120 million ($152 million).

Trends to Watch

"Overall, we see a significant increase in production capacity, a tendency for consolidation in the market, and a move of major production capacities to low-cost regions," says Rolf Rolli, general manager of **Merck Biosciences** (www.merck.com), parent company of **EMD Biosciences** (www.emdbiosciences.com), which supplies the Novabiochem brand of reagents for peptide synthesis, including building blocks, resins, coupling reagents, and linkers in research and production-scale quantities.

Rolli points to Lonza's acquisition of UCB Bioproducts, its expanded production capacity in Switzerland, and its investments in China, as well as increased production capacity at **BCN Peptides** (www.bcnpeptides.com) and at **Bachem** (www.bachem.com) as examples of the upswing in the peptide industry in recent months.

Bachem's leadership described 2005 as an exceptionally successful business year and reported a 14% increase in sales in the second half of the year compared to the same

period in 2004 and a nearly 18% increase compared to the first half of 2005. "Sales of active pharmaceutical ingredients (APIs) increased by 7.3%," according to a company representative. "In particular, peptide generics and, to a lesser extent, new chemical entities contributed to this growth, while sales of nonpeptide generics slightly decreased."

Attempts by global competitors to gain market share by offering low-cost peptides has "changed the price structure in the market," says Rolli. "But, at present, most cannot offer reliable delivery of compounds at the required scale of production." Their capacities, however, "will come close to the established European and U.S. suppliers in the future."

Rolli highlights enhanced overall synthesis efficiency and advantages in the chemical construction of long peptides as key benefits of Novabiochem's pseudoproline dipeptide building blocks. They consist of amide-protected serine or threonine coupled to another Fmoc-protected amino acid. "By temporarily mimicking the shape of a proline and thus introducing a kink in the peptide backbone, these serine or threonine derivatives enhance synthesis efficiency by disrupting on-resin peptide aggregation."

The Market Landscape

"The competitive landscape has been significantly modified by the acquisition of UCB Bioproducts by Lonza," says Pierre Barthelemy, Ph.D., managing director of **Peptisyntha** (www.peptisyntha.com).

"This is a sign that consolidation is taking place, which was largely expected," Dr. Barthelemy adds. "There is an excess of capacity in large-scale SPPS (solid-phase peptide synthesis)," and, at present, a limited number of commercial peptide APIs that require large-scale production.

Double-Digit Growth

Peptide suppliers, from custom houses to cGMP peptide API manufacturers, are reporting an increasing number of quote requests and peptide projects across the pharma and biotech industries. As the peptides industry enjoys an uptick in demand for both custom synthesis and GMP peptide production, "the generic segment is also quite dynamic at this moment, as several peptides come off patent in the near future," says Dr. Barthelemy.

NeoMPS (www.neomps.com) is enjoying steady 10 % growth it its peptides business, according to Robert Hagopian, director of business development. As industry chatter hints at demands exceeding 100 kilograms for some peptide drugs in development, the company confirms that one of its pharma-based projects will soon approach those production quantities. Its Strasbourg facility will triple its capacity by late 2007.

PolyPeptide Laboratories (PPL; www.polypeptide.com) is also undergoing a period of expansion. Moving into an additional 10,000 sq. ft. of new space at its Torrance facility will increase the company's working area at that site by 30 % and will nearly double capacity.

Expansion is also under way in Scandinavia, and PPL is constructing a new facility in India.

Emphasizing the health of the custom peptides industry, Chris Bai, Ph.D., CEO of **American Peptide** (www.americanpeptide.com), says that his company's sales have grown more than 50% over the past few years, attributing the steady increase to big pharma's shifting focus to biopharmaceuticals, including peptide- and antibody-based drugs. The main benefit of having more protein and peptide drugs on the market and in clinical development for peptide producers has been a decrease in the price of raw materials, as demand has increased. This in turn allows pharma to develop peptide drugs at lower cost.

Earlier this year, American Peptide announced a manufacturing clinical supply agreement with **Affymax** (www.affymax.com) to produce cGMP Hematide, Affymax' peptide-based erythropoiesis-stimulating agent being studied in Phase II trials to treat anemia in patients with chronic kidney disease and cancer.

The evolution of the peptides business has, in many ways, paralleled that of the oligonucleotides market, with a shift in demand for higher throughput and larger number of peptides in small amounts, observes Sven Klingel, Ph.D., general manager biopolymers in the laboratory equipment division of **Thermo Electron** (www.thermo.com). This evolution has also included a move from simple peptides to complex molecules and longer peptide sequences.

In addition, researchers are asking for products designed for proteomics research, such as Thermo's HeavyPeptide kits for relative or absolute quantification of proteins by mass spectrometry.

Klingel notes strong demand for very high-purity (>95%) peptides, with short delivery times becoming increasingly important. Customers are also looking to peptide providers for technical advice and support regarding peptide chemistry. Market pressures to lower costs and improve production efficiency are driving an "ongoing need for radical process optimization, sourcing optimization, and automation to maintain profitability," Klingel says.

"Customers are asking for full service antibody production," he adds, rather than obtaining peptides and corresponding antibodies from different suppliers. Thermo offers a combination peptide antibody prediction service with subsequent peptide antibody production.

Strides in Vaccine Research

"We clearly see an increasing demand for larger numbers of peptides at smaller scales," says Holger Wenschuh, Ph.D., managing director of **JPT Peptide Technologies** (www.jpt.com). Fueled by global vaccine development efforts, targeting HIV, SARS, and bird flu, for example, this demand derives from the need for thousands of peptides to

screen entire proteomes for peptide-based biomarkers and to identify B-cell and T-cell epitopes for vaccine design. The company supplies peptide arrays, complex peptide libraries, and custom peptides and peptidomimetics.

JPT's patented SPOT synthesis methodology assembles peptides by dispensing droplets of amino acids onto membranes. Solid-phase synthesis proceeds within these microreactors to yield tens of thousands of individual peptides. In addition to PepSpots custom peptide membranes, the company offers PepStar custom peptide microarrays on glass slides, RepliTope microarrays for mapping immunodominant regions on antigens, and other peptide array products.

Micro-Scale Peptide Sets contain up to one million individual peptides in amounts of 50? nmole/peptide in 96-/384-well plates. These sets can cover an entire pathogen proteome. In its ImmunoTools program, JPT is using these peptide sets for T-cell and B-cell epitope discovery. The company plans to have available a set of 70,000 peptides in the third quarter of 2006 that will cover the entire Mycobacterium tuberculosis proteome. Peptide sets for other proteomes, such as human cytomegalovirus and Chlamydia pneumoniae, will follow at the end of the year.

Also, noting an upswing in demand for peptides from vaccine researchers, Stacey Hoge, senior product manager for custom peptides and antisera at **Sigma-Genosys** (www.sigma-genosys.com), describes increasing requests for overlapping peptide fragments to cover an entire protein for epitope mapping applications or for the identification of binding regions.

"With higher-throughput and more affordable peptide manufacturing platforms now available, customers can order hundreds of peptides at reasonable rates to do screening studies that were previously cost prohibitive," says Hoge. The average cost per peptide has dropped from $400–$500 to about $50.

Innovative Technologies

Hoge points to two overall needs in the custom peptide production industry: to develop new synthesis platforms that would shorten cycle times and increase throughput, and to expand and improve options for high-throughput peptide purification. As an alternative to HPLC, Hoge describes efforts to develop tag-based affinity purification methods that would be amenable to high throughput.

With a growing customer base for its microwave-assisted Liberty peptide synthesis system, launched in the second quarter of 2005, **CEM** (www.cem.com) has placed more than 60 systems in academic and industrial research labs. The high energy levels achieved with microwaves kinetically excite the growing peptide chain, promoting elongation, while preventing unwanted aggregation of hydrophobic amino acids during chain extension.

The main advantages of microwave-driven synthesis are accelerated cycle times and enhanced purity with fewer deletion sequences as a result of reduced aggregation. Because synthesis times are shorter, microwave energy may also reduce side reactions and impurities, according to Michael Collins, president and CEO of CEM.

Racemization of amino acids due to the high energy levels present in microwave-assisted synthesis has not proven to be a drawback of the technology. Collins explains that although increased racemization can occur with cysteine and histidine couplings, lowering the temperature in the synthesizer when adding those amino acids eliminates the issue. Once attached, the amino acids are not able to racemize, as this is limited to the activated ester form.

CEM has also focused on minimizing aspartimide formation and by substituting piperizine for piperidine for aspartic acid activation for standard Fmoc deprotection steps, has been able to nearly eliminate aspartimide formation of susceptible Asp-Gly sequences. An additional benefit of substituting piperizine is that unlike piperidine, piperizine is not a controlled substance.

Microwave energy has also been used for high-purity synthesis of longer peptides, such as the 1-42b-amyloid (68.8% crude purity, 19 hours) and the 68-mer chemokine SDF-1a (50% crude purity, 35 hours), as well as for the synthesis of mono and poly phosphopeptides, polyamides, and difficult side-chain modifications.

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A peptide researcher at **Hoffmann-La Roche** (www.roche.com) who is using CEM's Liberty system for routine peptide synthesis points to speed of synthesis as the main benefit. Microwave energy enables overnight synthesis of a 30 amino acid peptide, compared to a three-day timeline with conventional peptide synthesis.

CEM is in discussions with companies to apply microwave technology to production-scale peptide synthesis. Collins predicts developments in large-scale peptide synthesis within two to three years.

Ongoing exploration of using microwave-based synthesis to ligate peptide fragments to form long peptides or proteins, and work underway to synthesize phosphopeptides, add fluorescent tags to peptides, and create other types of modified peptides will further expand the applicability of microwave synthesis.

The Future Looks Bright

The cost of manufacturing peptides has come down mainly because of reductions in the cost of raw materials, according to Jane Salik, Ph.D., CEO of PPL. At the same time, advances in purification technology have improved scale-up capabilities.

"The issue for bulk peptide manufacturers is the availability of raw materials," says Rodney Lax, director of sales and marketing at PPL. In particular, the newer protected amino acids are often difficult to obtain in large quantities or are exceptionally expensive.

Activotec(www.activotec.com) leverages its IP position in chemical peptide modification to produce custom peptides for research and drug discovery applications with an emphasis on long, cyclic, and other difficult to synthesize peptides.

With about 250 peptide candidates in clinical development in the U.S., the future looks bright, according to Chris Littlewood, CEO of Activotec. The company holds patents for proprietary modifications of the peptide backbone and is able to carry out solid phase peptide synthesis in the N-terminal to C-terminal direction, enabling the preparation of peptide analogues with C-terminal modifications and peptide bond modification. This method yields no detectable racemization and is amenable to automation, according to the company.

Working under a two-year research grant from the British government, Activotec is developing a novel method for de novo synthesis of highly pure therapeutic proteins, using polyethylene glycol as a temporary solubilizing agent in the sequential chemical ligation of synthetic peptide fragments.

Littlewood highlights the company’s recent success developing stable, active analogues of glucagons-like peptide 1 (GLP-1).

In addition to the importance of pricing and quality, "speed is the essence of the business," says Dr. Barthelemy. "Due to the complexity and length of synthetic processes for peptides, the catch-22 is to supply material within a short timeline and still develop the process in such a way that the chemistry is cost-efficient and robust for scale-up in the long term."

Most APIs are manufactured using traditional solution-phase synthesis. However, there is a move toward hybridsequential solid and solution phase synthesisstrategies, as costs of solid-phase peptide chemistry continue to decline. Expect this trend to continue, as demand for long peptides steadily increases. With hybrid synthesis, small peptide fragments produced with solid-phase synthesis are then joined in solution to form longer peptides.

The choice of synthesis strategy is primarily driven by economics and feasibility issues related to a particular peptide project.

"The future is likely to be a landscape where all three possibilities coexist," says Dr. Barthelemy. Peptisyntha recently completed construction and validation of two additional GMP suites at its Torrance, CA, facility, dedicated to solid-phase synthesis. It has budgeted funds to add medium-size capacity for solution-phase synthesis at its Brussels, Belgium site.

An emerging trend in the peptide API arena is the FDA's apparent tightening of purification specifications, with expectations approaching those in place for small organic molecules. "Impurities will be a hot topic," with the need to keep levels low, even as production quantities increase, says Hagopian of NeoMPS. Whereas accepted levels of impurities had been >0.5%, the trend has been toward the need to identify impurities that exceed 0.1%.

"We need guidelines from the FDA for peptides," says Hagopian. We are seeing this same kind of shift in Japan and Europe, he adds, and the consensus appears to be moving toward 0.1%.

Whether for research-grade or GMP peptides, product purity and quality will remain front-burner issues. Unfortunately they recently garnered front-page attention as well, with charges of mail fraud and false statements filed in May against SynPep, accused of falsifying data supporting the purity of peptides supplied by the company between 1999 and 2004.