POLYPEPTIDE LABS PHOTO

WET OR DRY **PolyPeptide uses solution-phase methods, shown here, and solid-phase techniques to synthesize peptides at its Torrance, Calif., facility.**

A PEPTIDE SPECIALIST

PolyPeptide Laboratories sticks to what it knows in pharmaceutical chemicals

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Even in the specialized world of pharmaceutical chemical production, PolyPeptide Laboratories stands out. The company operates five facilities in the U.S. and Europe, all of which are focused on just one thing: pharmaceutical peptide manufacturing.

PPL's devotion to this area of expertise seems to be paying off. The company is generally regarded as one of the world's top three bulk peptide producers, and it so far has survived an onslaught by larger multipurpose fine chemicals companies that see peptides as an attractive niche in a mostly slow-growing field.

PPL can trace its history back to the 1950s, when drug companies began extracting natural peptides such as adrenocorticotropic hormone (ACTH) from animal organs. Later came peptide synthesis through the solution- and solid-phase coupling of amino acids into peptide chains of up to 45 links.

PPL was formally created in 1996 when the European peptide synthesis arms of two drugmakers joined and became an independent firm. Soon, two other European facilities were brought into the group, and a U.S. unit was formed by Jane Salik, then a vice president at peptide manufacturer Bachem California, and her colleagues, the peptide chemistry experts Nagana A. Goud and Michael Verlander.

Today, the PPL Group is a privately held company that employs more than 300 people worldwide. Salik, who is president of PPI's U.S. operation in Torrance, Calif., and is on its executive management board, says the group's annual sales exceed $80 million, making it by her reckoning the number two peptide manufacturer after Switzerland-based Bachem.

Salik says PPI's sales have been growing at double-digit rates in recent years, a fact she attributes both to her firm's successful manufacturing track record and to a new wave of peptide therapeutics that are coming through drug company labs and starting to hit the market.

"Not only are peptide projects interesting to smaller biotech firms, but big pharmaceutical companies are looking at peptides as well," she says. Moreover, whereas large firms traditionally entered peptide therapeutics via partnerships with a biotech company, they are increasingly getting involved on their own, she adds.

In addition to ACTH, the first wave of peptides included calcitonin, an osteoporosis drug; oxytocin, used to induce labor and one of the first chemically syn-

thesized peptides; and desmopressin, a treatment for excessive thirst or urination.

Although peptide therapeutics boast advantages such as high potency and low toxicity, a big drawback is that most must be administered by injection. As a result, patient compliance problems emerged in the 1990s that caused drug industry interest in the field to wane somewhat.

More recently, though, new controlled-release, nasal, and inhaled delivery forms have made peptides more palatable to patients. AstraZeneca's Zoladex LA, for example, is a cancer therapy that can be injected once every three months because its peptide ingredient, goserelin, is wrapped in a slowly biodegrading polymer.

Rodney Lax, PPL's director of sales and marketing, also credits the approval and large-scale manufacture of Fuzeon, a peptide-based HIV treatment developed by Trimeris and Roche, for boosting peptide awareness. "The Fuzeon project has helped companies to recognize that big peptides can be economically manufactured on a very substantial scale," Lax says. The sheer quantity of raw materials consumed by Roche at its Boulder, Colo., plant—more than 100 tons per year—has also helped bring down prices of peptide raw materials, he adds.

OF COURSE, nothing attracts drug companies like potentially large markets. The early peptides were either hormones or closely related to hormones, and thus tended to treat exotic endocrine disorders or endocrine-dependent cancers. Today, Salik says, peptides are in development in almost every drug category, including anti-inflammatory, gastrointestinal, and antiobesity.

One peptide developer—and PPL customer—is Zelos Therapeutics, which is developing Ostabolin C for treatment of osteoporosis and psoriasis, both multi-billion-dollar markets. Spun off in 2000 from Canada's National Research Council (NRC), Zelos has raised close to $60 million in venture capital.

Paul Morley was studying the chemistry and biology of parathyroid hormone at NRC in the mid-1990s when he and his colleagues realized that analogs of the hormone had the potential to treat osteoporosis. He joined the Zelos spin-off, becoming chief technical officer, and soon embarked on a search for a manufacturer that could produce the peptide to current Good Manufacturing Practices (cGMP) standards.

According to Morley, Zelos immediately gravitated toward the "big three" in peptide manufacturing—PPL, Bachem, and UCB Bioproducts—because it wanted to work with a single firm that could be its partner from laboratory-scale production all the way through Phase II and Phase III manufacturing.

Morley says he liked PPL's long experience with peptide chemistry and the fact that it could produce in multiple countries. But mostly, he says he liked PPL employees such as Verlander, who has 25 years of experience in peptide manufacturing. "There's not really rocket science involved," he says of peptide manufacturing. "These are standard solid-phase synthetic mechanisms being used, and it's a matter of trying the right approaches to get the yields and efficiencies that you need."

Zelos' experience with PPL since then has been favorable, Morley reports. Ostabolin C recently entered a Phase II clinical trial with a PPL-made product, and PPL has completed development of a manufacturing process that can take the compound, which contains 31 amino acids and features a lactam bridge, to commercial launch. Separately, Zelos is working with the drug delivery firm Nektar Therapeutics to develop an inhalable powder form of its peptide.

Thanks to the needs of customers like Zelos, PPL is in the process of expanding peptide production capacity at its cGMP plants in California and Malmö, Sweden. By 2006, Salik says, the "multi-million-dollar" projects should boost U.S. capacity by more than 30% and Swedish capacity by almost that much.

PPL isn't the only company investing in peptide manufacturing, however. Fine chemicals giant Lonza recently announced it will spend $20 million to add to peptide capacity in Visp, Switzerland. And companies like UCB and SNPE's NeoMPS unit have been expanding as well.

For Lonza and some other multipurpose pharmaceutical chemical companies, peptides go hand-in-hand with oligonucleotides, a family of therapeutics made by combining nucleotides just as amino acids are linked in peptides. Oligonucleotides are at the heart of drugs in currently popular research fields such as antisense, RNAi, and siRNA.

According to Lax, PPL's management board has tossed around the idea of entering oligonucleotide manufacturing. "The chemistry is very similar, so there's no reason why we couldn't do it," he says.

Management, however, might want to consider the opinion of Zelos' Morley, who likes the fact that PPL is a specialist's specialist. "When the lure of oligos and antisense and siRNA came along, PolyPeptide didn't change," he says. "They were formed on their expertise in peptides, and they stuck with that." ■