As they seek to increase business with emerging drug firms, large contract manufacturers are encountering well-entrenched competitors particularly those that have made acquisitions — find themselves with manufacturing capacity to spare and are happy to make their own small-molecule pharmaceutical chemicals.

Faced with this reality, top contract manufacturers like Lonza, DSM, and Avecia that once dealt mostly with major drugmakers are increasingly turning to smaller virtual and emerging drug companies as a source of new business.

Many of these companies are exciting, entrepreneurial places with rich new product pipelines. As the big contractors knock on their doors, however, they are finding that such firms are already being served.
With all its money from financial backers and no products on the market, Targacept is hardly a member of the big pharma club. But as William Caldwell, vice president of drug discovery and development, likes to say, Targacept also isn’t a company run by “two professors in a garage.”

What Targacept is is an emerging pharmaceutical company with an interesting heritage and enviable financial backing. That’s because, although on its own for only three years, it is rooted in decades of research on nicotine conducted by R. J. Reynolds Tobacco Co.

That work resulted in hundreds of scientific papers and abstracts, many of which focused on neuronal nicotinic receptors, a class of molecular targets in the body that maintain and adjust nervous system activity. Research by Reynolds scientists and others suggested a role for these receptors in the treatment of human diseases.

Targacept was formed in 1997 as a Reynolds subsidiary to commercialize these findings.

Today, thanks to more than $120 million in investment from Reynolds and other backers—including a $60 million second round of venture-capital financing completed last month, the second largest in biotechnology in more than a year—Targacept has chemistry resources that many other emerging drug firms can only dream of. Yet it’s a significant customer of the contract manufacturing world as well.

Targacept’s first foray into pharmaceutical chemical outsourcing came in the mid-1990s when, while still part of Reynolds, it needed product to support clinical trials. Outsourcing went on hiatus while the firm sought partners to leverage that early work, and the firm didn’t return to the market until 2000. “Since then, we’ve gone full tilt with multiple programs and multiple contractors,” Caldwell says.

Third parties supplement Targacept’s own well-staffed laboratories, located in Winston-Salem, N.C. According to Caldwell, the company supports a computer-aided molecular design team; an eight-chemist medicinal chemistry group that conducts parallel synthesis and standard medicinal chemistry; a six-member process chemistry group carrying out chemical development, scale-up, and route selection and optimization; and a four-chemist analytical group that supports the medicinal and process chemists while performing bioanalytical work such as pharmacokinetic and in vitro metabolism studies.

by smaller contractors like Seres Laboratories, Cedarburg Pharmaceuticals, and Tetronics that don’t intend to be pushed aside.

Two process group members are dedicated to managing outsourcing of chemistry services and process development. “We believe that management of outsourced work should be a core competency,” Caldwell says. “We’ve been very deliberate about how we’ve built this out.”

Targacept has contracts with a half-dozen or so third-party suppliers that help manufacture small-molecule compounds, notably for three drugs in clinical trials and five in preclinical trials. Of these relationships, Caldwell points to one with Siegfried, a midsized pharmaceutical chemicals company based in Zofingen, Switzerland, as being particularly strong.

He says the two firms linked up through a fairly typical route—Siegfried’s response to a competitive bid on a Targacept compound.

The ties increased in August 2002 when Targacept acquired its first commercial drug, Inversine (mecamylamine HCl), a Merck-developed hypertension treatment that is known to modulate nicotinic acetylcholine receptors. Siegfried, it turned out, formulated the finished dosage form of Inversine at its Zofingen facility.

“But for Caldwell, Siegfried’s real draw has been that it is "very interested in developing relationships. They see an opportunity for long-term potential, not just one-off projects." As evidence, he points to the Swiss company’s recent response to a request to make a compound using a route developed in Targacept’s labs.

“They did it, but they also put a chemist on the compound and came up with another route that was cheaper and faster. That impressed me,” Caldwell says. “I wish other companies would display that kind of initiative.”

His advice to other potential outsourcing partners is that relationships are very important—for Targacept as well as other emerging drug companies. “We want to work with a service provider that shares a sense of passion to get our drug to market,” he says.

Caldwell definitely doesn’t appreciate the occasions in which a Targacept project has been pushed to a contractor’s back burner to make room for work from a major drug company. What he does appreciate are companies willing to take risks on compounds that aren’t on the market yet but that—he is confident—will get there. “Don’t see us as what we are today; see us as what we will be tomorrow,” he says. “We will be big.”

For many of these emerging pharmas, the project is their only one; it’s their baby. ... We help nourish and bring the baby into the world.”

Although their business model is evolving, big drug firms still typically conduct most drug development and scale-up in-house, outsourcing production only occasionally.
and only when commercial success seems ensured.

Emerging drug companies, in contrast, generally have limited internal production capability. Out of necessity, they will outsource small volumes of many promising compounds. Only a select few of these compounds move on to clinical trials, and even fewer survive to become successful. Many companies fail along the way. Executives with the small contract manufacturer serving these firms question whether large contractors will have the patience to put up with dozens of nibbles and misses in the hopes of landing the big product that succeeds.

Charles M. Boland, executive vice president of Cedarburg, a 50-employee contractor in Grafton, Wis., explains that the typical emerging company has a big drug discovery effort, some process development capability, and very little manufacturing, quality control, quality assurance, or analytical expertise. “Their needs are different from major pharma,” he says. “They outsource many activities that the majors do internally.” Companies like Cedarburg often provide regulatory expertise, quality assurance, and even the assembly of the chemistry, manufacturing, and controls sections for investigational new drug (IND) and new drug application (NDA) submissions to the Food & Drug Administration.

Boland and James G. Yarger, Cedarburg’s president, are both former Amoco employees who got the idea for their company while working in Amoco’s new ventures unit. They had wanted to outsource production of a compound, Boland says, and found very little competent pilot-scale capacity in the U.S. that complied with current Good Manufacturing Practices (cGMP) standards.

THEY BROKE GROUND on a facility in Grafton in July 1997, and by June 1998 they were operating a pilot plant and process development facility. Today, the company is the contract manufacturer of active pharmaceutical ingredients (APIs) for five commercial drugs and for multiple APIs in all stages of clinical trials. Boland says its customer base is roughly 70% emerging companies, 20% major pharma, and 10% generics firms.

He acknowledges that the larger companies are starting to compete more actively for emerging company business but says Cedarburg is holding its own, including winning out on projects in competition with much bigger firms. Working in its favor, Boland says, is a track record with difficult chemistry, successful GMP production and FDA inspections, and an entrepreneurial culture similar to that of the small companies it generally serves. “Because Cedarburg is the size it is, we can be much more responsive to customer needs,” he says.

NURTUREDAlthough Tetronics serves mainly small firms, it built up expertise working with the major player Abbott Laboratories.

Nitin Parekh, a vice president with DSM Pharma Chemicals—perhaps the largest contract manufacturer—counters that it’s not size that matters so much as the perception of size. “When working with smaller companies, we must organize our larger company in a way that meets the smaller company’s needs,” he says. This includes naming a project manager who acts as the customer’s interface with the entire DSM organization.

Although DSM’s emphasis has been on commercial-scale manufacturing for the major drugmakers, Parekh notes that it has a solid history of working with emerging companies as well. He recalls calling on GelTex Pharmaceuticals, a specialist in nonabsorbing polymers, as early as 1997 when the firm had just a handful of employees.

At the time, GelTex had identified colesevelam HCl as a polymer that could bind and remove bile acids in the bloodstream, causing the liver to draw cholesterol from the blood to replenish the bile pool. However, GelTex was having difficulty manufacturing the complex polymer—poly(alylamine HCl) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide—in significant quantities.

DSM SIGNED a development agreement with GelTex and began experimenting with the compound by drawing on its inhouse polymer expertise. “It was hard work even for DSM and required using the entire DSM organization,” Parekh says. “A small company might not have been able to solve the problem.”

However, DSM succeeded in scaling up the synthesis and began making the polymer in Linz, Austria, for use in GelTex’ clinical trials. Colesevelam was approved by FDA in 2000 and is now marketed as WelChol by Sankyo Pharma. GelTex was acquired by Genzyme in 2000.

DSM also has a deal with Cubist Pharmaceuticals, a small biotech firm for which DSM makes the antibiotic daptomycin, intended for the treatment of infections caused by gram-positive bacteria. FDA accepted Cubist’s daptomycin NDA in February under its priority review program and said it will act on the application by June 20.

Hubert Stückler, senior vice president of global sales and marketing at DSM Pharma Chemicals, says DSM pursues emerging companies not because it is interested in their clinical-trial-scale business but because it increasingly sees emerging companies’ compounds becoming commercial realities—often with the help of the larger firms that are DSM’s traditional customer base. “We look very carefully at the chances of success of an emerging company before we step into a relationship,” he says.

The Cubist and GelTex deals notwithstanding, Stückler acknowledges that a concerted focus on emerging companies is a recent phenomenon at DSM. It was only last year, for example, that it put in place a dedicated group of account managers that focus on such firms, he says.

However, the company is moving rapidly to increase the services it can offer small companies. Last month, it acquired a 30% shareholding in Syncom, a Dutch contract research organization specializing...
CV Therapeutics: Building A Relationship With Dow

V Therapeutics reached a major milestone last month when the Food & Drug Administration accepted its New Drug Application (NDA) for ranolazine, a potential treatment for chronic angina that works by partially inhibiting fatty acid oxidation. If approved, the drug will represent the first new class of antianginal therapy in more than 20 years.

The FDA acceptance is the latest in a string of successes for the 12-year-old firm. After acquiring ranolazine from Syntex in 1996, CVT has steadily moved the drug, trade named Ranexa, through the clinical trial process, providing angina sufferers with hope for a new treatment and convincing investors that CVT stock is a good buy.

It’s not important to angina patients or investors that CVT sources the drug’s active ingredient from Dow Chemical. But it’s of great importance to employees like Peter M. Strumph, vice president of operations. Palo Alto, Calif.-based CVT has no commercial production facilities and relies on Dow for ranolazine supply. For Strumph and his colleagues, it is crucial that the facilities where its lead drug is made pass rigorous FDA inspections.

CVT’s relationship with Dow began in 1998. The purchase from Syntex had included ranolazine manufactured for previous clinical trials, and CVT quickly contracted with another third party for supplies to conduct further trials. But as the drug continued to perform, Strumph’s team began to look for a contractor that would be able to carry it through late-phase trials and into commercial production.

CVT is unique in the pharmaceutical world in that its focus is on only one therapeutic area—cardiovascular disease. The company also develops only small-molecule drugs—partly, Strumph notes, because it has more leverage in the competitive small-molecule manufacturing market than it would if it were developing protein-based pharmaceuticals, where a handful of contractors dominate.

In keeping with its small-molecule outsourcing strategy, the company set up four hurdles for prospective manufacturing partners. The first is a successful regulatory quality track record. “The lack of a good regulatory and quality history—or the impression on our part that a company isn’t willing to continually invest in its quality systems—is a go or no-go criteria,” Strumph says.

The second is an appropriate equipment fit. The third is that a supplier have process development and analytical capabilities. CVT operates a 20-employee chemistry laboratory where it conducts route selection synthesis and bench-scale manufacturing, but Strumph says the firm looks to its vendors for assistance with process development.

The fourth—and perhaps highest—hurdle is that the supplier has successfully navigated the complete process of developing and manufacturing a new pharmaceutical chemical. “We want manufacturers that have worked in clinical development—done process development, documented that process in an NDA, and defended their quality systems in a preapproval inspection,” Strumph says. “Those are all steps we need to go through, and we want to make sure our contract manufacturer has gone through them as well.”

Dow was one of a handful of firms to emerge at the end of this winnowing process and, after subsequent interviews and negotiations, was hired by CVT. Samantha Janisse, CVT associate director for process development and manufacturing, became CVT’s main liaison with Dow, and the multyear task of process development and production scale-up began.
Although Janisse has a primary counterpart at Dow—Program Manager Jeff Legge—she explains that CVT takes pains to develop and maintain a relationship with multiple points of contact. “We wanted quality control to talk to quality control and process development to talk to process development,” she says.

Ranolazine development took place in three main stages. The first was a six-month effort that started with transfer of a technical package and ended with production of initial quantities at Dow’s Midland, Mich., site under current Good Manufacturing Practice conditions. The second leg, also about six months, took the molecule through process development to pilot production. The third, nine-month leg included additional development work, commercial scale-up, and manufacturing.

Janisse says the multistep commercial synthesis of ranolazine is “very straightforward,” thanks in part to streamlining efforts by Dow chemists and engineers during the development effort. She adds that Dow’s materials processing expertise was crucial to optimizing the manufacturing process.

Because ranolazine is a fairly high-dosage drug intended for a chronic disease, it must be made at facilities that can handle large-volume manufacturing. Indeed, Dow is conducting the final synthesis step in 4,000-gal reactors, producing metric tons per batch.

Strumph says CVT is open to working with smaller contract manufacturers on future lower-volume products, but he discounts the notion that a smaller contractor better understands or interacts with an emerging company like CVT. “There’s a lot to learn from a big company like Dow,” he says. Janisse adds that the melding of CVT’s creative, small-company culture with Dow’s well-defined, work-process-oriented mind-set can pay dividends for both. “It improves Dow and it improves CVT,” she says.

Explain the company began to study the emerging pharma market two to three years ago when its traditional business began to be crimped by the twin influences of declining new drug approvals and rising numbers of competitors.

Among Lonza’s responses were the plan to build the small-scale plant, announced in early 2002, and the creation last fall of a new business development position in the company’s Midland, Mich., site under current Good Manufacturing Practice conditions. The second leg, also about six months, took the molecule through process development to pilot production. The third, nine-month leg included additional development work, commercial scale-up, and manufacturing.

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In contrast with Lonza’s major pharma customers, which have more manufacturing flexibility, Kuo observes that the emerging companies he is calling on want to firm up their supply chains early on in the drug development process. This means working with them on early-phase synthesis projects of the sort that can be conducted in the new small-scale plant.

Larger firms are also potential customers of the small-scale plant, Pont notes, but honesty and effort, he says CVT will bring people to the project who can work well with others both inside CVT and outside the organization.

“We try to get our manufacturers to share our pride for the science, the clinical results, and the positive impact the drug can have for real patients,” Strumph says. “We endeavor to blur as much as possible any boundaries between the two organizations. You can’t write this into a contract, but it’s as much of a success driver as any technical skill set.”

It’s a lofty goal, but Strumph says he has a very down-to-earth reason for setting it. He wants everyone at the contractor—from the plant operator to the bench chemist to the lawyer negotiating the contract—to see CVT’s project as their number one priority.

“I want all the people involved to feel a sense of ownership in our project,” he says. “In the end, we get better service and a better product.”

Many big pharmaceutical companies find themselves with manufacturing capacity to spare and are happy to make their own small-molecule pharmaceutical chemicals.

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Larger firms are also potential customers of the small-scale plant, Pont notes, but they are typically “tactical” outsourcers of early-phase chemistry—using third parties selectively to supplement wide internal capabilities.

Kuo acknowledges that winning the confidence of smaller companies will be a challenge for Lonza. His ambition is modest: to patiently build relationships and plant seeds for future business. “A lot of personal trust needs to be built,” he says.

“But after that, Lonza has all the rest.”

Less patient Lonza competitors like Degussa and Avecia have jump-started their business with emerging companies through acquisition.

For Degussa, it was the 2001 acquisition of Laporte and its Raylo Chemicals contract manufacturing unit in Edmonton, Alberta, that provided the increased exposure to the emerging pharma market. Raylo is one of the oldest players in pharmaceutical chemical synthesis, formed in 1963 by the late Raymond U. Lemieux, then a carbohydrate chemist at the University of Alberta. Raylo started out doing...
research on penicillins for Bristol-Myers Squibb and later developed some of the first antiviral compounds for the National Institutes of Health. Laporte acquired Raylo in 1988.

Despite Raylo’s early ties to a major drug company, Commercial Manager Greg Klak says its business today is almost exclusively with small and start-up drug companies. Degussa’s European contract manufacturing sites, in contrast, are much more closely aligned with major pharma.

Klak says Degussa has maintained the Raylo name and identity because a lot of emerging pharma business is obtained by word of mouth. “It’s a small world, and if you do a good job for someone, they’ll tell everyone they know,” he says. “If you don’t do a good job, they will tell even more people.”

Typical of Raylo’s business is its seven-year contract with Vancouver-based QLT to manufacture verteporfin, the active ingredient in QLT’s Visudyne for wet age-related macular degeneration. Visudyne was discovered by QLT scientists and championed by Julia Levy, an immunologist and QLT founder, whose mother lost her sight to the disease in the early 1990s.

Although QLT today calls itself Canada’s largest biotechnology firm, Klak says it was “truly a virtual company” when Raylo began working with it in 1989, at the very earliest stage of Visudyne development. “They realized that they had a compound that looked promising, but they came to us for expertise,” he says.

Visudyne entered clinical trials in 1993 and received its first approval in 1999. Marketed by Novartis, it is an injectable drug that is carried to the eye by lipoproteins in the bloodstream. When a laser is shone into the eye, the drug releases a singlet oxygen, destroying abnormal blood vessel cells and stopping damaging leakage.

In general, Klak says, smaller companies—like QLT in its early years—seek more guidance from a contract manufacturer than does a big drugmaker. Raylo doesn’t tell customers how to run their businesses, he says, but it will advise them on what processes work efficiently. Some customers, in turn, actually send personnel to “live with” their project at Raylo’s Edmonton site.

“For many of these emerging phar- mas, the project is their only one; it’s their baby,” he says. “Customers rely on our expertise and experience. We help nourish and bring the baby into the world.”

Peter Jackson, vice president for pharmaceutical products at Avecia, explains that as a one-time unit of ICI and sister to the Zeneca drug business, his company is rooted in the world of big pharma. That connection was cemented with Avecia’s 1999 spin-off from AstraZeneca, he says, because AstraZeneca took all the early-phase chemistry infrastructure, leaving Avecia mainly with facilities geared toward late-phase clinical trials and commercial production.

However, Avecia soon became determined to pursue the early-phase business
and began studying how to replicate that infrastructure for itself. “The question was whether to build or buy, and we concluded that the necessary flexibility and speed of response would be difficult to build,” Jackson says. The result was Aveca’s 2000 acquisition of the Canadian chemical development house Torcan.

At the time, 95% of Aveca’s small-molecule synthesis business was with major drug companies, Jackson says. Torcan’s customer base, in contrast, was virtually all start-up firms and small companies. He sees synergy occurring, as evidenced by the $6 million scale-up in Huddersfield of a small company’s product that was first made by Torcan. “It’s one of several that we see feeding through in the next few years,” he says.

Although Aveca’s new early-phase plant in Huddersfield houses small-scale equipment similar to that at Torcan, its typical customer is the major drug company that wants to see a development process quickly translated into clinical-trial quantities of a pharmaceutical intermediate or active. What the two facilities have in common, Jackson says, is a full plate of projects and chemists fully booked well into the second half of the year. “It’s an opportunity-rich environment in early phase,” he says.

One of the pioneers of the early-phase business is Jan Oudenes, who joined Torcan in 1982 as one of its first employees. He became president in 1990, when Torcan had a staff of 30, and oversaw its subsequent growth into the 150-employee firm that Aveca purchased. Oudenes left last year and is now head of Alphora, a consulting firm that helps emerging drug companies move products out of the research lab and into the marketplace.

Oudenes says that for large companies like Degussa and Aveca to make their acquisitions pay off, they must maintain the service-oriented culture that made their new units successful suppliers of early-phase chemistry in the first place. This is no easy task, however, because the early-phase services required by emerging companies are fundamentally different from the late-phase and commercial manufacturing that major drug firms outsource.

“One early phase is about service at every level,” Oudenes says. “It requires a flat organization in which lots of people have direct contact with the customer. The mentality is to be able to do another product every week. Large-scale manufacturing requires a top-down model, often with a single point of contact. Economies are important, pricing is important, planning and scheduling are important, long campaigns are important.”

LARGE CONTRACTORS argue that customers want a “one-stop shop” where they can buy both kinds of production. Plus, the large firms are counting on leads from the early-phase business to become big projects in their commercial business.

But Oudenes points out that there is a clear transition point between Phase II and Phase III of the drug development process. Emerging companies that make it to Phase II often look for major pharma partners to take them through Phase III and commercial launch. “That point is a natural place for manufacturing to switch,” he says—either to one of the partner’s plants or out to bid. “It’s all about the right development at the right time.”

Oudenes does acknowledge that large companies can provide benefits to small customers. For example, they may have access to technology that can help emerging firms develop difficult compounds. And they can introduce a rigor to the development process that some emerging firms desire. But he cautions that an early-phase services business must be kept at arm’s length in a big company. “Unless it’s carefully managed, the model won’t work,” he says.

In an effort to nurture a separate culture for its relationships with emerging companies, Siegfried Ltd., a Swiss contract manufacturer, took a novel approach: In 2000, it formed a new stand-alone business unit called Siegfried Ventures. Richard F. Haldimann, director of business development for Siegfried Ventures, is based in San Diego, heart of the West Coast biotechnology universe (see page 67). Haldimann explains that Siegfried opened the new business out of necessity.
“Siegfried Ventures grew out of the realization that emerging pharma would drive innovation,” he says. “We saw that if we wanted to be in contract manufacturing, we had to focus on this area. But although Siegfried had dealt with global pharma for 25 years, we didn't understand emerging pharma.”

Just a few people work in Siegfried’s San Diego office, but Haldimann says being in the region is helping the company learn the market, adjust its services to serve it, and build credibility with potential customers.

“Earlier this month, the company hosted a two-day symposium in San Diego on drug development in the biotech industry. Speakers came from big drug companies such as Pfizer and Wyeth as well as start-ups like Targacept and Momenta Pharmaceuticals. The offices are complemented by a $25 million pilot plant that opened last summer at Siegfried’s Zofingen headquarters. Dennis Bauer, vice president of U.S. business development, says the pilot plant eliminates a bottleneck, providing the sort of early-stage manufacturing capability that big drug companies enjoy but that many emerging firms lack.

Bauer adds, however, that the pilot plant doesn’t signal an effort by Siegfried to become a player in the business of making small quantities for the very early phase market. The firm’s bread and butter remains commercial manufacture. “A quick 300 g for a toxicity test—can we do it? Yes,” Bauer says. “Is that the target of our sales and marketing efforts? No.”

Although Siegfried Ventures is only three years old and accounts for less than 1% of overall Siegfried sales, Haldimann considers it a success. Its emerging company customers include Targacept, a spin-off of R. J. Reynolds Tobacco Co. that is developing drugs that act on neuronal nicotinic receptors, and Juvantia, a Finnish company that is developing a treatment for levodopa-induced dyskinesia in Parkinson’s disease. Juvantia’s drug, fipamezole, was granted fast-track designation by FDA in November and is now in Phase II studies at NIH in Bethesda, Md. Siegfried is one of the few contract manufacturers to offer finished-dosage-form production and is in discussions with Juvantia to provide this service as well.

Small companies that have their production plans worked out, Haldimann notes, are in better shape when it comes to the licensing or acquisition negotiations with major pharma firms that often seem inevitable in the drug business. “If you control manufacturing, you control the fate of your drug,” he says.

In contrast to many of the other large companies active in contract manufacturing, Dow Chemical has taken no special steps to cultivate ties with emerging small-molecule drug companies other than to concentrate resources in this area. But according to Nick Hyde, business director for Dowpharma, that’s because Dow already had strong bonds to such firms.

He attributes this to Dow’s past ownership of the drug company Marion Merrell Dow. Although MMD was sold in 1995 to what was then Hoechst, Dow kept its plants, chemists, and engineers. When Dow launched a contract manufacturing business later that year, Hyde says, it attracted smaller U.S. drug companies because it was a local supplier and it had experience with final APIs and the quality assurance, quality control, and regulatory issues that go along with making them.

“We understand the drug development process and the importance of building parallel paths of commercial scale-up into the project pipeline,” Hyde says. “We make clinical supplies available and plan for scale-up contingencies if drugs are successful.” The typical contract manufacturer, in contrast, is a European fine chemicals firm that started working with multinational drug companies. Hyde notes that these big drugmakers handle their own regulatory affairs and generally contract out only pro-
duction of advanced intermediates, keeping the final reaction step to themselves. Developing an API for a small company without regulatory expertise is no small leap for such a contract manufacturer. “Our competitors have had to figure out things we’ve been doing for 20 years,” he says.

Today, Hyde says, more than half of Dowpharma’s business is with smaller companies. Examples include GelTex, for which Dow makes RenaGel, a polymeric phosphate absorber for kidney dialysis patients; Human Genome Sciences, for which Dow used chelation technology to help develop a protein-based drug that can deliver radioisotopes to malignant cells; and CV Therapeutics, for which Dow makes ranolazine, the active ingredient in Ranexa, a treatment for chronic angina. FDA accepted CVT’s new drug application for Ranexa last month.

Although there’s no doubt that the biggest players in contract pharmaceutical manufacturing are pursuing business with emerging drug firms, smaller contractors maintain that they aren’t being scared off. Case in point is Tetrionics, a 45-employee firm based in Madison, Wis., that has focused on virtual and emerging companies almost exclusively for the past two years.

THE IRONY, according to Michael Czarny, vice president for business development, is that Tetrionics got its start supplying Abbott Laboratories, one of the drug industry’s heavyweights.

Tetrionics was formed in 1989 to build on expertise in vitamin D chemistry developed at the University of Wisconsin, Madison, laboratories of Hector F. DeLuca, now chair of the school’s biochemistry department. Abbott approached Tetrionics in 1990 for help in scaling up production of paricalcitol, a vitamin D analog that Abbott had developed for treatment of hyperparathyroidism.

Tetrionics worked with Abbott through the 1990s, performing process development, analytical method development, and validation work on the drug’s 27-step synthesis. It added regulatory and quality-control departments as the drug entered clinical trials. And in 1996, it moved into new facilities at the University of Wisconsin Research Park that provided isolated manufacturing and R&D areas.

The drug, trade named Zemplar, was approved by FDA in 1998, and Tetrionics remains Abbott’s exclusive API supplier. But since the approval, Czarny says, the company has moved again—to even larger quarters—and has pursued new busi-
ness mainly with emerging companies; it has roughly 25 of them as customers today.

According to Czarny, those customers are a broad cross-section of the emerging pharma landscape. “We get everything from a structure on the back of an envelope to a 6-inch binder,” he says of the technology packages that Tetrionics receives. “Some customers have a good understanding of the regulatory requirements and the steps they must take, and others are not so experienced.”

Tetrionics President Peter O. Johnson argues that because the company is located near the University of Wisconsin and draws top chemistry graduates, it enjoys the resources and brainpower necessary to serve a start-up drug company. Top students generally have their pick of employers. Graduates that choose Tetrionics, he says, are looking to work in an entrepreneurial environment that “lets people make things happen early in their professional careers.”

Czarny adds that this spirit is held in common with emerging pharma companies, some of which are wary about working with a larger outsourcing partner. He relates an instance in which Tetrionics was competing against a big custom manufacturer for the business of an emerging oncology drug company: “The executive vice president told me that his people were concerned about getting lost in a large company,” Czarny says.

In the end, though, he says Tetrionics won the business the old-fashioned way: by offering advantages on the price of the project, the quality of the product, and the timetable under which it could get the job done.

Mark Frishberg, vice president for business development at Seres Laboratories, a 20-employee custom synthesis firm in Santa Rosa, Calif., agrees that speed of response is a natural strength of a small company. He relates an experience from the recent Informex trade show in New Orleans in which an executive he knew from a small pharmaceutical company approached him with information on a compound it had licensed and wanted to have made. “We contacted his lawyer and within 10 minutes had signed a confidential disclosure agreement with changes,” Frishberg relates. “In 10 more minutes, he had our feedback on the technical package. A big company usually can’t do that.”

And Frishberg should know, having joined Seres in July 2002 after a long career in R&D and business with Eastman...
Since joining Seres, Frishberg says he has been enjoying his interaction with a wide range of emerging companies that have an equally wide-ranging knowledge about scaling up pharmaceutical chemical production. Some of these companies bring syntheses, developed in academic settings, that use hazardous solvents or include steps that simply won't work on the kilogram scale. Frishberg says. Or their processes make heavy use of chromatography, which can be expensive or impractical in a commercial-scale manufacturing process.

At the same time, he attests to a heightened sense of responsibility in his new job. Many of his customers are developing compounds that, while perhaps small in volume, are intended to cure untreatable diseases. And some of these firms don’t have a lot of margin for error.

“When it comes to service, both big and small companies want it yesterday,” Frishberg observes. “But if a big company doesn’t get it yesterday, it can adjust. If a little company doesn’t, it can be out of business.”

In the decade or so before Eastman Chemical was spun off, Eastman Kodak operated a small-scale contract manufacturing business in Rochester, N.Y., and a commercial business in Kingsport, Tenn., and Batesville, Ark. Frishberg says the pilot-scale business had managers that assumed the risk and found a way to make money by developing projects and passing the successful ones on to the commercial unit.

THE CATCH, he says, is that it can take years and many ups and downs for an emerging firm to be successful, and managers in big companies often don’t have the patience and stomach for that kind of wait. “Big firms have the resources and capabilities to succeed, but do they have the continuity of management and purpose? Will they consistently put the priority on a project when a small company needs it?” Frishberg asks. “The answer is generally no.”

On the other hand, small projects are a small firm’s bread and butter. Frishberg notes that about 70% of Seres’ business is with emerging companies whose needs can be met with Seres’ up to 100-L scale equipment.

INNER WORKINGS Ancillary equipment is isolated at Siegfried’s new pilot plant in Zofingen, Switzerland.

Chemical. Having worked both sides of the fence, he says his experience is that a large company can overcome its natural inertia and successfully serve emerging drug companies—as long as top managers are committed.

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