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Contained Chemistry

Synthesizing highly potent compounds is a lucrative and growing niche for custom chemical manufacturers

By Ann M. Thayer

Leveraging the ever-improving understanding of disease along with new technologies for discovering molecules with medicinal powers, pharmaceutical research has been hitting upon increasingly potent compounds, ones that work at doses of less than 10 mg. Compare this to a typical 325 mg dose of aspirin. More effective drugs are good news for patients, since smaller doses can mean fewer side effects.

Steroids, hormones, prostaglandins, and chemotherapeutics are examples of drugs typically classified as potent. Of these, new cancer drugs are generating the most interest. In fact, 750 cancer therapies are in development, according to a new survey by the industry group Pharmaceutical Research & Manufacturers of America. They include targeted drugs, potent chemotherapies, and highly potent cell-killing or cytotoxic agents conjugated to delivery molecules.

Oncology is already one of the largest drug product sectors, accounting today for about \$48 billion in global sales, reports the market research firm IMS Health. The sector is growing 12–15% per year, or more than twice as fast as the overall pharmaceutical market. That's why custom chemical suppliers that can manufacture potent compounds for drug industry customers occupy an attractive niche. And those with conjugation expertise sit in an even more appealing niche within the high-potency area (see page 28).

Given these prospects, more and more contract chemistry firms are advertising their high-potency manufacturing capabilities. Whether such claims are warranted is a sore spot for many contractors, who aren't happy about the proliferation of small-scale suppliers. Others say there is room in the market for all. "Many custom manufacturers are investing in this area," says Enrico T. Polastro, vice president and senior industry specialist with Arthur D. Little Benelux, noting that demand continues to be strong.

Custom manufacturers themselves estimate that active pharmaceutical ingredients (APIs) for oncology products account for up to 30% of drug development projects. And IMS predicts that 25 to 30 new chemical entities for oncology will be introduced by 2012. Those figures look promising to suppliers that have the manufacturing muscle, and many are bulking up through acquisitions and expansions.

Success isn't ensured, however, since a company must achieve critical manufacturing standards, most importantly keeping workers safe and products uncontaminated. For the workers involved in manufacturing highly potent APIs,

acceptable occupational exposure limits (OELs)—or the airborne concentration of material averaged over eight hours, considered safe for a majority of healthy workers—can be as low as nanograms per cubic meter.

In order to determine the potential risk of exposure, companies set their own limits by looking at a compound's pharmacologic potency, toxicity, and other effects. Although there's some disagreement about what is occupationally "potent," the drug industry typically uses that rating for compounds with OELs at or below $10 \mu\text{g}/\text{m}^3$; for those that are highly selective for a receptor or enzyme inhibition; and for those that may be carcinogenic, mutagenic, or teratogenic at low doses.

Complicating definitions further, each drug developer or manufacturer uses occupational exposure bands (OEBs) in the absence of OELs for early stage compounds. These OEBs or occupational health categories use potency and toxicity criteria to determine the control measures they'll employ. In a four-band system OEB 3 usually corresponds to a $10 \mu\text{g}/\text{m}^3$ OEL; manufacturing products that are OEB 3 or higher requires special "engineering controls," or containment technologies. OEB 3 also tends to be the default band when information on a compound is limited.

The use of control bands has grown over the past 20 years, notes John P. Farris, president of SafeBridge Consultants in Mountain View, Calif. In the late 1980s, when he was employed by the steroid producer Syntex, Farris participated in an industry-led effort that established the OEB process and tried, unsuccessfully, to unify the bands. He formed SafeBridge in 1998 to offer toxicology, industrial hygiene, and analytical chemistry services around potent compounds. Since then, he says, SafeBridge has determined OEBs for more than 2,500 compounds, the majority of which fall into band 3 or 4.

Many companies use SafeBridge's four-band system, or a five-band alternative that Merck & Co. safety professionals published in 1996. Under the Merck system, drugs that fall into band 1 require conventional current Good Manufacturing Practices (cGMP), whereas band 5 specifies no human intervention. "You can use any system you want, but it should be adapted for your company's products and work environments," Farris says.

He also recommends keeping any system simple. "Then people will understand it and are likely to use it," he explains. These systems are key risk communication tools that immediately tell an operator what to expect and how to proceed, he points out. Whatever system companies use, they'll likely synthesize potent, cytotoxic, or otherwise dangerous compounds in contained environments.

For small-scale synthesis, containment in a ventilated enclosure or simple glove box alone may suffice, whereas larger procedures can involve equipment fitted with special valves or glove boxes for direct charging of discharging materials. At even larger scales, manufacturers use isolators—sophisticated glove box-like chambers that can be integrated with bigger vessels or equipment—or even

environmentally controlled rooms and facilities containing a combination of these equipment types.

Nonpotent drugs often are produced by the ton. Because highly potent drugs are used in much smaller amounts, facilities usually considered "pilot scale" or smaller may be large enough to produce commercial quantities of a few kilograms per batch and up to a few hundred kilograms per year. Polastro says annual world demand for potent chemotherapies, such as irinotecan or topotecan, is tens of kilograms. For cytotoxics, such as doxorubicin, an adequate annual supply is just 1–10 kg.

When a pharmaceutical company assesses which custom chemical makers have what it takes for high-potency manufacturing, the differentiating factors include facility design, containment level, analytics, monitoring capabilities, and operational scale, along with procedures, training, and experience. The package of services often includes dedicated labs for R&D and quality control.

"There are contenders and there are pretenders," Farris says, and drug developers need to know the difference when evaluating suppliers. In recent years, the words "potent drug manufacturing" have been appearing all over tradeshow booths. "Did these people just spring up overnight?" he asks. "Some did and some have been working at this for a long time and understand it."

For example, Farris and others in the industry say simply isolating a room and putting workers in protective suits doesn't qualify as containment. "The room by itself cannot be containment," he says. Instead, the process equipment must be contained so that there are no releases to the workroom when materials are transferred between vessels. "And protective suits are only redundant, not primary, protection. Anything else is not acceptable," he adds. "The contenders understand this."

Much of what's been done to define and handle these biologically potent materials has been undertaken by industry. At present, Food & Drug Administration guidelines only address cross-contamination as it relates to product quality and safety; worker safety falls under the purview of occupational health regulators. In Europe, however, drug regulators also consider worker and environmental concerns when they inspect a facility, Farris says. Regulatory moves are afoot internationally to require dedicated facilities for certain classes of compounds, such as cytotoxics and reproductive hormones.

Some producers of potent drugs, especially those in Europe where changes are coming faster, already operate this way. In response, pharmaceutical industry groups are promoting the use of risk-based assessments to determine what manufacturing strategies, and physical and procedural controls, adequately allow for multiproduct, rather than dedicated, facilities. An example is the International Society for Pharmaceutical Engineering's Risk-based Manufacturing of Pharmaceutical Products (Risk-MaPP) program.

High-potency production expertise had long resided in-house at the major pharmaceutical companies. But as part of the drug industry's recent manufacturing consolidation, a few firms have shed some capabilities. In the U.K., Merck sold a plant to Aesica Pharmaceuticals and Pfizer sold a facility to India's Piramal Healthcare. Roche, which bought Syntex in the mid-1990s, sold a former Syntex site in Mexico to Dr. Reddy's Laboratories.

Boehringer Ingelheim Chemicals (BIC), the API-producing arm of the German drug company, is particularly active in the high-potency field, supplying highly potent APIs for both its parent and outside customers. In 2006, the containment and monitoring practices at BIC's Petersburg, Va., plant were certified under SafeBridge's Potent Compound Safety assessment program.

Switzerland's Helsinn Advanced Synthesis makes the highly potent anti-nausea drug palonosetron for its parent, Helsinn Healthcare, and marketing partner, Eisai. Since 1999, the contract-manufacturing unit has operated a 600-L high-potency plant and in 2006 it added a 20-L plant for 50–500-g batches. It already can manufacture hundreds of kilograms and may add another 600-L unit or a large-scale plant for making 30–300-kg amounts.

Meanwhile, Switzerland-based Cilag, part of Johnson & Johnson's worldwide manufacturing network, is becoming more aggressive in pursuing work from third parties, says Hans Lehner, Cilag's general manager for chemical operations. Its four-year-old high-containment plant has three independent cGMP equipment trains operating at the 60-, 250-, and 400-L scales.

The Cilag facility can handle OEB 4 compounds, which under J&J's system requires worker exposures be no more than 500 ng/m³, and has achieved limits of 10 ng/m³ and below, says Urs Thurnheer, Cilag's director for scale-up and new product introduction. "It's a fully enclosed operation, so there is no open product from the discharging of raw materials to final dispensing of the APIs," he says.

As anyone who has ever used a lab glove box knows, working under contained conditions is awkward. Commercial-scale production of highly potent APIs has its own complexities and costs, thanks to the specialized equipment and the time- and labor-intensive nature of the work. Reactors, isolators, production suites, even entire facilities, may be devoted to a given product until production is completed, meaning only one product can be made at a time.

Processes may be modified to work safely and practically in containment. Chemists try to simplify and telescope synthetic routes as much as possible. For example, Thurnheer says, operators want to minimize the number of solid-product transfers they carry out, since these steps present the greatest risk for exposure. In contrast, handling liquids and slurries presents fewer concerns because they are less apt than powders to disperse in the air.

Once a product is made, however, the work is far from done. One of the most time-consuming aspects of high-potency manufacturing is cleaning to ensure

worker safety and avoid product cross-contamination, Thurnheer explains. The cleaning process can take weeks. And, from start to finish, the entire production process must be monitored to ensure that the containment measures are working.

At its plant in Schaffhausen, Switzerland, Cilag makes bortezomib, the API in the multiple myeloma drug Velcade. Developed by Millennium Pharmaceuticals, in Cambridge, Mass., the drug was licensed outside the U.S. to J&J. Detroit-based custom manufacturer Ash Stevens supplies Millennium in the U.S.

In the Cilag and Ash Stevens plants, as in many others, personal protective equipment has been supplanted by engineering-based safeguards. "People like having engineering controls much more than the older technology where they had to wear suits, which is a very uncomfortable work environment," says Stephen Munk, Ash Stevens' chief executive officer.

Still, some manufacturers use personal protective equipment along with engineering controls for extra precaution or as a last line of defense if there is a loss of containment. Overall, good ergonomics contribute to increased safety, managers say. And glove boxes are often designed to comfortably fit individual workers.

Accident rates can rise the longer operators must work in containment areas, so shifts may be shorter than in plants making conventional pharmaceutical chemicals.

Ash Stevens, which produces several highly potent anticancer compounds such as the nucleoside derivatives clofarabine for Genzyme's drug Clolar and 5-azacitidine for Vidaza (developed by Pharmion and now part of Celgene), also produces compounds for the National Cancer Institute. With vessels up to 500 gal, the company focuses on API volumes of less than 1 metric ton per year, Munk says. It recently installed two filter-dryers that can handle between 5 and 50 kg each.

Because of the operational challenges, custom manufacturers can charge premium prices for making highly potent APIs. Of course, production costs are higher too and it's not clear if the high-potency manufacturing business offers better profit margins. Either way, custom manufacturers say demand for these services is strong.

For similar operational and cost reasons, many pharmaceutical firms are outsourcing their highly potent drugs. Some large drug developers have more projects than they can handle internally, or they don't wish to support specialized production facilities for small-volume products. Others simply are outsourcing more. And small drug companies without manufacturing capabilities are a large customer group.

To get into the business, several custom chemical firms have acquired high-potency operations. Aptuit gained its three-suite facility with its 2006 acquisition

of EaglePicher Pharmaceutical Services. Likewise, Albany Molecular Research Inc. fully acquired Organichem in 2003. According to AMRI, it can handle materials with OELs under $1 \mu\text{g}/\text{m}^3$ in reactors of up to 1,200 L and batch sizes of 50–100 kg. AMRI recently added a non-GMP high-potency development lab to accommodate increased customer orders.

In late 2007, Germantown, Wis.-based Cambridge Major Laboratories acquired ChemShop in the Netherlands and has already started expanding the high-potency kilolab and pilot-plant facilities there. The company can handle compounds at a SafeBridge OEB 3 or Merck 4 level, says Peter Van Tilburg, president of CML Europe. It just commissioned two new cGMP suites with up to 100-L capacity for producing hundreds of grams at a time to support customers' early development work.

"Because the quantities are smaller, a lot of companies think this is easier to do," Van Tilburg says about high-potency manufacturing. "But it's a completely different ballgame—you need different people, different expertise, different equipment, and different motivation." For these reasons, companies won't succeed simply by throwing a lot of money at building capacity, he says. Nor will those who invest a nominal amount in limited equipment, says another manager, adding that "it's not enough just to buy a glove box and say you can do high potency."

Some companies clearly rank as the large-scale producers that can take highly potent products beyond the lab and early clinical trial stages. "We see a lot of competition at the smaller scale with people adding kilogram suites," says Aslam Malik, president of Ampac Fine Chemicals (AFC), based in Rancho Cordova, Calif. "In 2007, we made over 2 metric tons of several different highly potent APIs."

Operating with OELs as low as $0.2 \mu\text{g}/\text{m}^3$, AFC has three facilities with reactors ranging from 20 to 200 gal and has been producing commercially since the early 1990s. In 2004, the company added a six-75-mm-column simulated moving-bed chromatography unit to its smaller high-potency facility, and in 2006 it upgraded a larger facility. Malik says he's considering further expansion in 2009.

Larry Zeagler, AFC's executive director for commercial product management, also sees opportunity in noncytotoxic drugs outside the oncology area. These products likely would fall in an OEB 3 category, or maybe OEB 4, he says, which means containment will be required. The quantities would be larger than for highly potent APIs but less than for nonpotent ones. "There seems to be a need for more intermediate-scale manufacturing," he says.

Like AFC, Ferro Pfanstiehl Laboratories has been in this business for about 20 years. According to the company, it is able to produce toxic and cytotoxic APIs and intermediates in amounts up to 50 kg using reactors up to 300 gal.

In 2001, Ferro Pfanstiehl was initially SafeBridge certified. SAFC, part of Sigma-

Aldrich, became certified in 2002 at its Madison, Wis. site and in 2006 Almac Sciences in Northern Ireland passed the bar as well. Almac's certification included its engineering controls, cGMP kiloscale operations with containment to 0.1 µg/m³ for cytotoxic compounds, and its operating procedures and practices.

"Four companies have successfully gone through our program and have some element of SafeBridge certification," Farris says. At present, several other companies are looking at the certification process, which reviews 60 different criteria and includes an on-site assessment, with various levels of interest. "We're hoping to get the number of certified companies up to maybe a dozen over the next two to three years," Farris notes.

Although both large and small customers will audit a supplier's operation, large drug companies tend to take more notice of SafeBridge certification, company managers say. Not only may the bigger firms be more familiar with high-potency manufacturing, but they also have more established occupational health and safety staff who will evaluate contractors as part of their risk management activities.

Safebridge certification is "almost like a permit," says David Feldker, SAFC Pharma vice president for manufacturing and U.S. operations. "Knowing that we are certified at our site in Madison, Wis., gives customers the confidence that our engineering and personnel controls are in line with what is needed."

SAFC has made a big push into high-potency manufacturing. In 2004, it acquired the Madison-based firm Tetrionics. Since then, it has expanded capabilities for making highly potent small molecules and biologics. To carve out its sizable position, the company has invested \$45 million over the past 18 months, Feldker says.

SAFC just spent \$4.5 million to increase its cGMP pilot plant and large kilo-lab capacity in Madison. The expansion added two 400-L and two 100-L reactors, giving it capabilities for projects from development-scale up to commercial-scale. The company also installed solid-form testing and analysis equipment as part of its high-potency offering. And in St. Louis, SAFC has just added a suite to supply early-stage clinical-trial quantities of highly potent conjugated APIs.

SAFC's single largest investment is in a new facility in Jerusalem for fermentation-derived highly potent APIs, including secondary metabolites, cytotoxins, and proteins. The \$29 million cGMP plant is scheduled to be completed in early 2009, Feldker says, and will include 1,000- and 4,000-L tanks for large-scale bacterial and fungal manufacturing. Operating at OEB 4, SAFC hopes to obtain SafeBridge certification there, Feldker says.

SAFC is wagering on the high-potency area because of anticipated double-digit growth rates. "Many large pharmaceutical companies had held this technology captive but now are starting to outsource quite a bit more," Feldker says. About 80 or 85% of SAFC's high-potency projects are cancer therapeutics.

"We have over 350 projects for highly potent compounds with customers," Feldker says. For several years, SAFC has been the exclusive supplier of paricalcitol, the active ingredient in Abbott Laboratories' thyroid drug Zemplar. "We have several late-stage products and hopefully in the next year, if everything is working right, we'll have some approvals coming our way," he adds.

Lonza also is betting big, having announced about \$100 million in investments to add a commercial-scale conjugation facility and expand into large-scale production of potent APIs. A new 40,000-L facility in Visp, Switzerland, will be running in July, says Stefan Stoffel, head of operations for Lonza's exclusive synthesis business sector. It will be capable of handling compounds with OELs down to 1 $\mu\text{g}/\text{m}^3$.

The unit is designed for large-volume potent, but not cytotoxic, compounds. "We target producing four to six different products on an annual basis using one line," Stoffel says. "We definitely see some of them in tens of tons quantities that we can cover with the larger facility." Lonza also has two plants with 630- and 2,500-L reactors for producing commercial quantities of more potent drugs with OELs of less than 1 $\mu\text{g}/\text{m}^3$.

These facilities complement existing lab-scale capabilities for smaller quantities or even more highly potent compounds. "There is a limited group of companies that can make products in the variety that we can," Stoffel says. "We started up small and have expanded because of the steep increase in projects that we have in the pipeline." A majority of Lonza's large-scale capacity is committed to specific customers' orders, and it is already anticipating the construction of another train in the API plant.

Between 2006 and 2007, customer inquiries nearly doubled and the trend has continued, Stoffel says. Contracts for highly potent products, unlike traditional APIs, are often multiyear, single-supplier agreements. Two factors play into this: the small product volumes and the limited number of suppliers. Lonza already is producing five commercial products in the areas of oncology, immunosuppression, and veterinary medicine.

In early 2007, Lonza bought the biobusinesses of Cambrex, which included antibody production for a cytotoxic conjugate. Cambrex retained its small-molecule fine chemicals business, which has been active in the high-potency area for 10 years. The company just opened a five-suite development and kilo-scale lab facility for highly potent compounds in Charles City, Iowa, says Eric Neuffer, vice president for sales and business development. It also has large-scale 1,200-L equipment and can handle OEB 5, or 1 $\mu\text{g}/\text{m}^3$ levels.

Investing nearly \$12 million, France's Groupe Novasep opened a high-potency cGMP plant in Le Mans earlier this year. In addition to contained synthesis under OEB 5, corresponding to 0.1–5 $\mu\text{g}/\text{m}^3$ OELs, the company says it offers large-scale preparative chromatography for highly potent compounds. It specializes in the semisynthesis and purification of the anticancer agent paclitaxel and other

taxanes.

OmniChem, the Belgium-based firm owned by Japan's Ajinomoto, is expanding as well. It has added two production lines, each with 800- and 1,600-L vessels. The addition allows it to handle projects ranging from lab scale up to 250-kg batches in 6,000-L reactors. Except for this largest scale, which operates at a $1 \mu\text{g}/\text{m}^3$ exposure limit, OmniChem's containment level is $0.1 \mu\text{g}/\text{m}^3$.

Meanwhile, Uquifa, the pharmaceutical division of the British firm Yule Catto, is a relatively new entrant to the high-potency area, having added its facility outside of Milan, Italy, about two years ago. The company can handle compounds with OELs of $1\text{--}10 \mu\text{g}/\text{m}^3$, says Charlie Johnson, Uquifa's head of sales and marketing. Along with development labs, its production capabilities include 250- and 1,200-L reactors to make 5- and 50-kg lots.

"Associated with our high-potency unit is a pilot plant for the upstream stages of synthesis," Johnson explains. "The idea is to bring convergence to the synthesis so that the potency is built into the molecule late in the process and the upstream stages can be handled in a conventional plant."

Uquifa is targeting oncology products, including cytotoxics, and some newer cytostatic drugs, Johnson says. "There is a distinct trend in the drug industry to move away from traditional chemotherapeutic agents, such as cytotoxics and oncology hormones, to more targeted therapies," he points out. Although these drugs are not highly potent or toxic but rather specific for disease targets, they still will have to be produced in contained facilities.

According to the market research firm Datamonitor, sales of cytotoxics will grow about 1% per year over the next few years and then start to decline. Several high-profile cancer drugs—topotecan (GlaxoSmithKline's Hycamtin), irinotecan (Pfizer's Camptosar), temozolomide (Schering-Plough's Temodar), gemcitabine (Lilly's Gemzar), capecitabine (Roche's Xeloda), and docetaxel (Sanofi-Aventis' Taxotere)—have or will come off patent in the next five years and fuel the generics market. Sales of antihormonal cancer therapies are already falling.

Meanwhile, sales of small-molecule cytostatic drugs, which stop cancer cells from multiplying and include, for example, tyrosine and aurora kinase inhibitors, will grow at double-digit rates.

"Our strategy is to target late Phase II through to commercialization," Johnson says. Phase II clinical trials, where drug efficacy is starting to be tested, is a preferred capture point because a supplier can bring its chemical development expertise to bear before a process gets locked down. "Phase II is also usually the point at which the toxicology profile becomes more mature, so we can make a fuller assessment of the molecule and really start to build a scientifically justifiable occupational exposure limit." Up to this point, because the volumes are small, compounds usually can be safely handled in glove boxes.

The drug company may provide the toxicology and other data to the

manufacturing partner or may simply inform the partner as to what control band it believes is needed. Custom manufacturers say they often will conduct this analysis again or even get an outside, independent assessment if there's any ambiguity or disagreement.

"Ultimately, it's our responsibility, because if we are going to be manufacturing these products it's our duty to protect our personnel," Johnson says. The OEB also determines whether a product must be manufactured in a high-potency plant at an associated higher cost.

Custom manufacturing firms are accustomed to optimizing processes. But unlike in traditional API synthesis, manufacturers of highly potent compounds don't typically emphasize yield or tweaking a process during scaleup in pursuit of every penny of savings. It's hard enough to get processes to work under contained conditions, and the small-volume products are less cost-sensitive anyway. As such, large-scale, low-cost assets don't necessarily make a company more competitive.

Although competition from low-cost Asian producers is not yet a factor in highly potent, custom-made APIs, many Western suppliers say they anticipate that it eventually will become a factor. Many older anticancer drugs are generic products, such as doxorubicin, Polastro points out, and Asian generic drug firms are playing a role. For example, Dr. Reddy's and Ranbaxy Laboratories in India are touting their high-potency manufacturing capabilities.

For now, a few Asian custom manufacturers have bought or built high-potency capabilities. In 2005, India's Hikal opened a small plant, and Piramal Healthcare acquired Avecia's U.K.-based business. In 2007, Piramal added a high-potency conjugation suite in Scotland, where it already had five OEB 4 or 5 suites for making cytotoxics, cytostatics, and conjugates.

"We see a lot of growth opportunities in the small-molecule and finished dosage formulations areas," says R. Ananthanarayanan, president of Piramal Pharma Solutions. Depending on what scale plant it finds it needs, the company is considering expanding production for highly potent small molecules in either the U.K. or India.

Carbogen-Amcis, which was acquired by India's Dishman Pharmaceuticals & Chemicals in 2006, also bridges geographies. It operates established lab- to medium-scale facilities in Switzerland and is building a high-potency facility in Bavla, India, which is scheduled to open in early 2009.

"In Switzerland, we go up to 630 L for high-potency manufacturing, and this facility will be a very nice crossover," says Carbogen CEO Mark Griffiths. "It will go from 630 L up to 1,600 L, with the capacity to go larger." The facility will operate under Carbogen's own OEB 3 (less than 10 $\mu\text{g}/\text{m}^3$) and OEB 4 (less than 0.3 $\mu\text{g}/\text{m}^3$) limits.

Carbogen, which has been in the high-potency business since 2002, is responding to increasing customer demand and capacity restraints, Griffiths says. "Demand is very strong and the reality is you won't win projects unless you create the capability," he explains. "You have to have the capabilities to show customers, and then they will come. Most companies are not going to make a financial commitment to you until they see the facility and understand how you are going to run it."