

### One-Pot Synthesis Aids Scale-Up and Data Collection

One of the main goals in chemical processing is to minimize the number of vessels used—thus reducing the number of vessel-to-vessel transfers, the amount of vessel cleanout required, and ultimately time and effort. To address this need, a new suite of products from Argonaut Technologies (Foster City, CA) provides automated “one-pot” synthesis for chemical development. In addition to reducing the number of vessels used, the tools provide more-complete data findings and greater process efficiency through a straightforward scale-up path.



The Advantage Series 3400 process chemistry workstation

“When process chemists are developing a method to prepare a pharmaceutical product, they will review the unit operations and try to cut out any unnecessary steps or reduce synthesis to one pot,” says Owen Gooding, the director of the Chemical Development Group at Argonaut.

The Advantage Series product suite, which comprises the Advantage Series “2050” manual chemistry synthesizer,

the “3400” process chemistry workstation, and the “4100” process scale-up reactor, can be used to perform each function of the chemical development process for pharmaceutical research and manufacturing, including the route-scouting, screening, optimization, and validation stages.

Each product in the suite is a bench-top synthesizer and can operate automatically or semiautomatically, which includes reporting data, logging all the thermal, pressure, and pH parameters into a file, and producing a report at the end of each experiment. The experiments are then captured in a 21 CFR Part 11-compliant format.

According to Gooding, pharmaceutical manufacturers are under increased pressure to achieve shorter times to market yet have to contend with molecular structures that are much more complex. “So the whole idea during process development is to gain a maximum amount of information with a minimum amount of experimentation,” says Gooding.

To streamline the process and ensure more-accurate results, each unit contains multiple reactors so that more experiments can be performed in the same amount of time. The equipment is also digitally monitored with various probes during the entire production run so that all data are recorded even if a technician isn’t physically present. The 3400 workstation, which contains four independently operating reactor vessels, basically functions as a mini pilot plant, allowing the operator to simulate large-scale projects while still at the bench.

“Manufacturers are able to obtain more data in a shorter period of time,”

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### Universities and FDA Collaborate to Reduce Cost of Manufacturing

The top 16 U.S. pharmaceutical companies spend more than \$90 billion on manufacturing each year, according to a *Wall Street Journal* article released 3 September 2003. This total—which includes materials, labor, operations, and depreciation of investments—accounts for more than 36% of the industry’s overall expenditures, and is more than double the annual spending



Jackson A. Nickerson



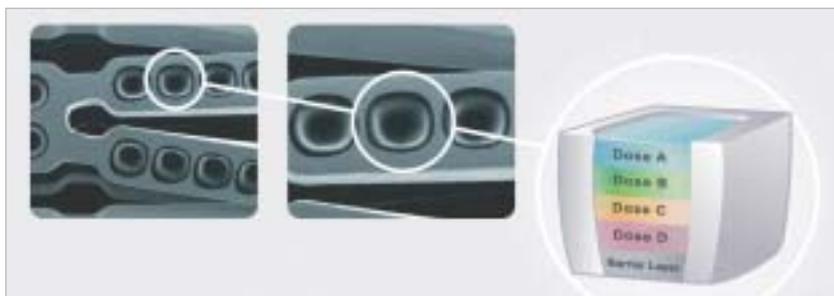
Jeffrey T. Macher

on research and development. A collaborative research effort between FDA, Georgetown University (GU, Washington, DC), and Washington University in St. Louis (WUSTL, St. Louis, MO) aims to tackle pharmaceutical manufacturing costs with a benchmarking study of manufacturers that will identify the most efficient, low-cost ways to organize pharmaceutical manufacturing.

According to one principle investigator, Jackson A. Nickerson of WUSTL, price manipulation and regulation have been tried in the past to drive down the costs of manufacturing, but he believes there is a better way to solve the cost problem. “If the regulatory system could shift a little and if manufacturers changed the way they managed their plants a little, the overall cost-saving might be as high as 25%,” he says.

The research project, lead by Nickerson and Jeffrey T. Macher of GU, is a two-part investigation funded by the Olin School of Business at WUSTL, the

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One or more drugs can be layered in one or hundreds of the reservoirs in Conor Medsystems' stents. (Courtesy Conor Medsystems).

## Drug and Device Camps Practice Art of Integration

In many respects, coronary stents are beginning to look more like drug-delivery vehicles than medical devices.

For example, Biosensors International USA (Newport Beach, CA) and X-Cell Medical Inc. (New York, NY) are creating a fully integrated drug-eluting stent company to develop products to deliver novel anti-restenotic drug candidates.

The agreement will combine Biosensors' expertise in drug and polymer synthesis, stent design, and catheter delivery systems with X-Cell's anti-restenosis drug discovery programs and compounds. X-Cell currently has multiple drug candidates in various stages of development for use with drug-eluting stents.

And, Biosensors and X-Cell are not the only companies jockeying to specialize in the robust stent marketplace, which by many analyst accounts is expected to double to \$5 billion by 2005.

A report by The Venture Capital Analyst (Wellesley, MA), *Drug-Coated Stents and Beyond*, published in October 2003, lists five young companies eyeing this opportunity:

- Allvivo Inc. (Lake Forest, CA), developer of a surface-coating technology that shields medical devices from immune-system attacks and makes it possible to layer therapeutics on the device. It is currently conducting animal trials of stents with its surface coating.
- Conor Medsystems Inc. (Palo Alto, CA), developer of the MedStent, which contains hundreds of drug-carrying wells; currently in clinical trials in Europe.

- Polymerix Corp. (Piscataway, NJ), developer of a polymer made of drug molecules and inert "linker" molecules that can be coated onto medical devices; plans a pig study of a stent coated with its polymer.
- Vascular Architects Inc. (San Jose, CA), developer of an approved PTFE-coated stent to treat peripheral vascular disease; company is considering coating the stent with an anti-restenosis drug.
- Xtent Inc. (Redwood City, CA), developer of a stent for treating diseased arteries that cannot be treated effectively by existing stents (e.g., blood vessels with long lesions and for lesions that occur in small vessels).

The trend could potentially throw open the question of the primary mode of action for future drug-eluting stents: some may be considered devices that carry drugs, as they are today, while others may be considered drugs having a novel delivery mechanism.

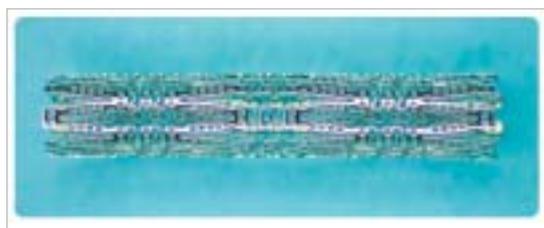
Purists will argue that the drug-eluting stent is a medical device carrying a polymer-drug mixture that adheres the drug to the device and controls its release into the body. Given that bare-metal stents preceded the

drug-eluting variety by nearly two decades, the purists may argue, the evolution is clear. Further, because the drugs are used to treat a condition brought on by the stents themselves—the restenosis or scarring of the vascular tissue caused by the body's response to the placement and presence of the stent—the drug clearly plays a secondary role in treating a patient's cardiovascular condition.

From a development, formulation and production perspective, however, the purist viewpoint may not prevail much longer. Report editor Brian Gormley cites the Conor Medsystems stent as a "drug-carrying platform," and the Xtent device as having the capability of serving as "a drug-delivery vehicle." Both appear to have the potential to tip the primary mode of action to the drug end of the spectrum rather than the device end.

For Biosensors and X-Cell, however, the goal is not to favor one end of the spectrum over another but rather to reap the benefits of both. "By combining these companies, we have a stent, a very good polymer, and a compound pipeline," says Jeffrey T. Barnes, a partner at Oxford Bioscience Partners (Boston, MA). Oxford is the founding investor of X-Cell, which is a product of the venture capitalist's cardiovascular

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Stents such as this investigational drug-eluting device from Conor Medsystems are evolving to improve their drug-delivery capabilities. (Courtesy Conor Medsystems).



Each reservoir on the Conor stent contains a proprietary barrier layer, which controls the direction of drug elution. (Courtesy Conor Medsystems).

## NanoCrystal Technology Targets Poorly Water-Soluble Drugs

An increasing number of drug candidates synthesized each year by pharmaceutical companies are considered poorly water-soluble. Most of these compounds are dropped from development because they can't be formulated properly. However, a new solution to poorly water-soluble drug candidates is now available and is aimed at improving bioavailability, dosage proportionality, and patient safety.

NanoSystems, a unit of Elan Corporation, plc (Dublin, Ireland), has created "NanoCrystal" technology to reduce the particle size of poorly water-soluble drugs and increase the rate of dissolution. The reduction occurs by transforming poorly water-soluble drug candidates into nanometer-sized particles—usually less than 1000 nm in diameter—through a milling process. The drug can then be incorporated into common dosage compounds such as tablets, capsules, inhalation devices, and sterile forms for injection.

"A poorly water-soluble drug will take a long time to dissolve in the gastrointestinal fluids, and if the rate of dissolution is very slow, the drug may not dissolve completely before it's eliminated," says Richard Vickers, vice-president of commercial licensing for Elan Drug Delivery Inc. (King of Prussia, PA). With NanoCrystal technology,

there is an increased amount of dissolved material, which, in turn, increases bioavailability.

The company also believes that the lower concentration of active drug molecules can increase safety for the patient. "The drug concentration is usually proportional to side effects," says Vickers. "Minimizing the exposure to the active drug molecules typically minimizes side effects."

Drug makers may also benefit from the use of NanoCrystal technology in drugs that must currently be taken with food. Because of the lower concentrations of active ingredients, FDA may, in the future, be willing to approve product labels that allow patients to take such drugs without restrictions. The lack of restrictions may be especially helpful for patients who take more than one medication per day at different times and have difficulty complying effectively because of complex dosing requirements.

NanoCrystal technology also promises to improve drug dosage proportionality. According to Vickers, it's common for poorly water-soluble drugs to have different corresponding bioavailability and therapeutic responses. For example, a response from 100 mg of a drug may not necessarily be twice the response of a 50 mg dosage. Instead, doubling a dosage may result in only one-third or one-quarter of the response. However, by improving dose proportionality, the drug level in the blood increases accurately, which makes the therapeutic effect more predictable.

NanoCrystal particles are actually small particles of drug substance, pro-

duced by milling, and then stabilized against agglomeration by surface adsorption of selected generally regarded as safe (GRAS) stabilizers. The result is a suspension of the drug substance that behaves like a solution.

Currently, there are two products on the market incorporating NanoCrystal technology. One is Wyeth's "Rapamune," a drug that is used for the treatment of transplant rejection and the other is Merck & Company's "Emend," a central nervous system drug which is currently approved for the treatment of nausea and vomiting associated with cancer chemotherapy. Emend is also in clinical trials for the treatment of depression. "One is a tablet and the other is a capsule," says Vickers. "However, any dosage form using a poorly water-soluble drug can benefit from the application of NanoCrystal technology." Some dosage forms currently in development from NanoSystems incorporating NanoCrystal technology include pulmonary delivery, intravenous or parenteral delivery, and other oral deliveries.

According to Vickers, the existence of poorly water-soluble drugs is a significant problem in pharmaceutical development, but has been somewhat unrecognized. "It's currently estimated that anywhere from 30% to 60% of the molecules that are developed through pharmaceutical companies' research and development efforts are poorly water-soluble," he says. "The pharmaceutical industry is looking at this technology to help make these molecules useful for product development."

*Doreen Coppola*

## Stopper Film Production Moves to the U.S.

West Pharmaceutical Services (Lionville, PA) has begun producing its FluroTec-coated vial closures (stoppers) in the United States. Previously, the coating and closures were manufactured in Japan by Daikyo Seiko Ltd., from whom

West licenses the Flurotec technology. The company believes that basing production in the U.S. will be preferable to customers who find it easier to conduct supplier audits domestically. West will continue to supply coated stoppers produced in Japan to those customers who don't wish to change their sourcing.

Flurotec is a fluorocarbon film made from a modified ethylene-tetrafluoroethylene (ETFE) polymer similar to PTFE (polytetrafluoroethylene, also

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The filling operation for a lyophilized drug. (Courtesy Lyophilization Technology, Inc.)



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says Paul Dreier, director of product development at Argonaut, "which allows them to make better decisions about what their next experiment will be."

Dreier uses the example that during research, the equipment will collect all kinds of data such as calorimetric data that might not be useful at that particular stage of the process. However, during scale-up, the fact that the calorimetric data has already been collected will reduce the number of tests required for the scale-up stage, thereby decreasing time to market.

Gooding adds that having calorimetric data collected early in the process also helps ensure safety. "Completely understanding the thermal aspects of the reaction early on can possibly eliminate potentially dangerous reactions earlier in the cycle and prevent developing a reaction that is inherently unsafe," he says.

Perhaps most beneficial, however, is that the same equipment used during research can also be used for the actual manufacturing of materials. "Manufac-

urers use the same equipment and the same software to further optimize their processes during manufacturing," says Dreier.

Argonaut itself uses the vessels to manufacture its own chemical consumables such as polymer-bound reagents and other products for synthesis and purification. According to Dreier, "Going from a multiple-stage process to a one-pot process saved us time and expense just as a pharmaceutical process optimization laboratory would optimize their processes to produce materials quicker with less cost."

Gooding, who directs the chemical development and manufacture of the reagents, agrees. "Combining the emerging technologies of automation and parallel synthesis in these instruments gave us the benefits of a shorter time to market, shorter product development cycle, and more information about the chemical processes faster."

Ronelle Russell



The Advantage Series 3400 workstation reactor

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McDonough School of Business at GU, and the National Bureau of Economic Research/Sloan Foundation. Basing their methodology on a research project that the pair participated in as doctoral students at the University of California, Berkeley, Nickerson and Macher will identify what factors lead to superior performance at manufacturing facilities. According to Nickerson, "The models we will develop have the potential to lower costs, increase profitability, increase the availability of drugs, and reduce the number of product recalls."

In the manufacturer-related section of the research project, Macher and Nickerson will survey more than 200 product and biological manufacturing facilities about their manufacturing procedures. Using a secure Web site, each participant will answer questions about the company's regulatory interfaces, internal management, products, production, technological sophistication,

and facility organization. The investigators will use the data to investigate whether certain factors play a role in a company's regulatory performance in terms of efficiency, product recalls, and product availability. Macher stresses, "Manufacturers are already producing high quality products, but we can improve the production and regulatory systems to make production times faster and resolve deviations more quickly."

The pair is currently recruiting participants for the project, and Macher says they have received an overwhelmingly positive response from manufacturers. "Every facility we have approached has signed on to be a part of the project because they see value in having this kind of data. The findings will help them understand how they can organize themselves more efficiently," he said. Upon completion of the project, each participating plant will receive a scorecard of how they compare with other anonymous plants. They will also

be given a road map that explains how they can get from where they are now in terms of manufacturing productivity to a more efficient system based on the team's statistical analysis.

In addition to their study of manufacturers, the researchers will collaborate with FDA on a separate study that will target identified risks to pharmaceutical quality. FDA, GU, and WUSTL have established a material transfer agreement that allows Macher and Nickerson to analyze confidential FDA information and to conduct research that will help FDA identify factors that predict manufacturing performance. The goal for this area of the research is to further refine FDA's risk-based site selection model for inspections.

Using data collected by FDA between 1990–1999, the researchers will examine both industry- and FDA-related factors such as the types and amounts of products that the plant produces, the size and age of the facility, and the FDA inspector's education, training, and experience. Macher and Nickerson will analyze this data to decide whether these factors predict regulatory outcomes such as product recalls, FDA inspection, and product availability. The findings will help FDA better manage its inspectorate.

According to Nickerson, both phases of the project are slated for completion in August 2004 so that they can provide input to FDA while they are still within the window of opportunity established by the agency's "Pharmaceutical CGMPS for the 21st Century—A Risk-Based Approach" initiative. As part of this plan, FDA has the ability to revise its regulations and the researchers hope to take advantage of this flexibility. In addition to publishing academic papers about the research, Nickerson says they hope their findings will have an impact on the way FDA allocates its resources and organizes its investigations of manufacturing facilities. In conjunction with increasing efficiencies and enhancing the agency's high standards for safety, Macher says, "Our goal is to help FDA rearrange the way it assigns investigations based upon the characteristics of the facility."

Kaylynn Chiarello

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device incubator called Accelerated Technologies Inc.

Barnes takes pains to point out that X-Cell develops its own compounds to capitalize on “the many pathways” available to treat coronary blockages. The compounds are “very different,” he says, explaining that the mechanism of action is different from that used in other drug-eluting stents. “We haven’t copied



Drug elution can be tailored over time from a few hours to a few months in the Conor stent. (Courtesy Conor Medsystems).

a compound,” he says. The compounds “fall into different categories” than the existing sirolimus or paclitaxel anti-restenotic compounds now in use. He adds that the X-Cell compounds are at various stages of development: some are being screened, some have already acquired animal data, and some are being evaluated for toxicity. “We are now focused on three or four classes of compounds,” says Barnes.

With compounds in development, X-Cell needed a polymer to get them formulated for use on stents. Barnes and company officials approached Biosensors and other companies. “At Biosensors, the relationship worked well,” says Barnes. “They had the stent and polymer, we had the compounds. We took the next step.”

At Biosensors International, chief technology officer John Shulze notes

that suppliers of drug-eluting stents often work with outside coating houses and pharmaceutical companies to develop their products. Biosensors has licensed the use of its bioabsorbable coating and its “S” bare-metal stent to Guidant Corp (Indianapolis, IN), for use with Everolimus (from Novartis Pharma) in Guidant’s Future I and II clinical trials.

Though the prevailing analyst view is that drug-eluting stents will garner a large and growing share of the overall stent market, some are not so sure. “Whenever a new technology is

introduced in an evolving market such as interventional cardiology, market dynamics change and new players emerge,” according to Amit Bohora, practice leader for medical devices at Frost & Sullivan (Palo Alto, CA). “One of the major challenges for the first mover is to generate enough awareness to expedite end-user adoption—in this case, convincing cardiologists to move from bare stents to drug-eluting stents.”

Bohora points out that preliminary data show “dramatic improvement” in outcomes relative to bare metal stents. But the studies show that stents do not save lives and they produce only limited cost savings. Skepticism about the adoption of drug-eluting stents is largely due to price sensitivity in the market and the fact that “clinicians remain more concerned about absolute reductions in

restenosis than relative reductions,” says Bohora.

Meanwhile, Biosensors has been working with X-Cell for about a year. Says Shulze, “For new compounds, we need to get the correct release profile,” he says, explaining that there are different pathways to pursue: how long the drug is resident; the drug’s concentration; and the design of the coating. “But the reciprocal is also true: properties of the coating may influence compound development.”

It is from this back-and-forth development process that the new X-Cell-Biosensors company hopes to create a viable business entity. “We’ll have all technology under one group, focused on delivering drugs to the treatment site,” says Shulze.

Adds Barnes of Oxford Biosciences, “the opportunity is not predicated on competing with the big players who already have approved drug-eluting stents or are approaching market approval: Cordis (a Johnson & Johnson company), Boston Scientific, Guidant and Medtronic Inc. You could potentially develop something a large player needs, or something better than what they have, or come up with something for a large player that addresses a clinical market not yet served—diabetic patients, for example.

The new combined company is expected to be operational by the end of the year. Though the current focus of the company is cardiovascular, Shulze believes some of the compounds may also be useful in other devices.

*George Miller*

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known as Teflon). FluroTec, Teflon, and silicone are some common coatings applied to vial closures to improve their machinability and to reduce extractables and leachables.

Whereas silicone is usually applied to stoppers by tumbling them in silicone oil, the ETFE and PTFE coatings are normally applied only to the bottom and top. The film is not applied to the flange or sides of the stopper, because the fluorocarbon coatings can reduce

the stopper’s flexibility, affecting how well it seals with the sides of the glass vial. “It’s the pliability of the rubber that makes the seal,” notes Narlin Beaty, chief technical officer at Chesapeake Biological Laboratories (Baltimore, MD). “So they leave that part uncoated.”

Coating the bottom of the stopper—the part that is in contact with the drug—reduces the risk of extractables, leachables and interactions between the drug product and the closure. Many industry experts note that the highest potential

for interactions exists with biological drugs. Notes John Shabushnig, PhD, a member of the Science Advisory Board of the Parenteral Drug Association (PDA), “We’re seeing a shift to larger molecules with biotechnology-derived drugs, and these can be more sensitive to chemical degradation than the older, small-molecular-weight drugs.”

Don McMillan, vice-president of marketing for West, points to the recent European recall of Johnson & Johnson’s

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anemia drug "Eprex" (sold in the United States as "Procrit"), as an example of the risk of closure-drug interactions.

Batches of the drug manufactured in Switzerland were recalled in August because of contamination resulting from chemical reactions between the drug and the rubber stoppers. The recall did not affect the drug manufactured in the United States.

McMillan believes that reducing risk is particularly important for smaller biotech companies. "In biopharmaceuticals, you have many companies whose entire livelihood depends on one drug," he says. "In cases like those, you would certainly want to use packaging materials that ensure the lowest possible risk of drug contamination."

Since many biotech drugs are also lyophilized, or freeze-dried, coatings are

also applied to the top of the stoppers. This coating is applied because after the liquid is removed from the drug in the lyophilization process, an upper shelf is lowered to push the stoppers all the way into the vials. The coatings help prevent the stoppers from sticking to the shelf during this step.

In fact, improving machinability is another benefit of stopper coatings. "This is very important for high-speed processes, where you may have closures being placed on vials at a rate of 300 per minute," comments Michael Akers, PhD, director of pharmaceutical research and development at Baxter Pharmaceutical Solutions (Bloomington, IN). "If you don't have a slippery stopper, you run the risk of having stoppages due to closures sticking to one another or not being able to move fast enough through the filling machines," he says.

Although silicone is a good lubricant, it also has some disadvantages, including the creation of particulate matter. "The quantities will not necessarily be enough to make it fail," notes Akers, "but it's very well known that silicone shows up in electronic particle-counting systems, and can also be reactive with proteins."

Beaty notes that his company has also tried another coating, an immobilized silicone, to improve machinability. "It's not intended to protect from leachables or extractables," he notes. "Instead, it's intended to make the stoppers machine better." One advantage is that this coating can be placed on the flange part of the vial. "Unfortunately you can't put fluorocarbon there," continues Beaty, "because then the flange can't perform its primary function well, which is to provide a good seal."

Laura Bush

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