Developers of Antibodies to SARS Look Ahead to Manufacturing Costs

With the outbreak of severe acute respiratory syndrome (SARS) now spreading globally, researchers under the mandate of FDA are attempting to generate human antibodies to combat the virus. The Massachusetts Biologic Laboratories (MBL, Jamaica Plain, MA) of the University of Massachusetts Medical School (UMMS) is partnering with Medarex, Inc. (Princeton, NJ), a biopharmaceutical company, to codevelop fully human antibodies to SARS. Although a marketable product from this research is still a few years away (human clinical trials are projected to begin in two years), the companies already are looking ahead to the challenges and costs of large-scale manufacture.

Nils Lonberg, PhD, senior vice-president and scientific director at Medarex, says that although manufacturing capacity is available through MBL's facilities as well as through contract services, a company like Medarex still faces challenges in manufacturing biologicals at a large scale. "The cost of goods is relatively high compared with other drugs," Lonberg says. "At this point, the technology exists to make antibodies cheap enough to make them competitive in the marketplace, but there's certainly room for improvement."

To reduce the costs of production, Lonberg explains that the industry needs additional technology development to extend the life of the fermenter run and to increase cell densities and the yield per cell. "These are all things that can bring the price down, in addition to cheaper media and cheaper column material for purifying the antibody," he says.

Lonberg also states that developing a high-yield process will affect time to market—a critical factor in the production of any drug. "Clinical testing for efficacy takes a long time, and the time it takes to develop a high-yield process often forces companies to go back and repeat clinical trials because they have changed aspects of their manufacture,"

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Indena Automates Paclitaxel Line

The Italian company Indena has installed new automation architecture at its manufacturing plant in Settala, Italy. The department where the new software was installed carries out the purification steps for the production of an active pharmaceutical ingredient for the oncology drug paclitaxel. With the new automation, operators will have greater control of manufacturing operations and equipment maintenance.

The new installation modernizes the Settala plant, which was built in the 1960s. In the past, automation at the plant was limited to individual instrument controls. Plant operators in the oncology line can now establish parameters and control the production process from one engineering workstation and four field operator stations, which are all protected by passwords.

Certain features influenced the selection of the automation. "The system seemed to be expandable," noted Valter Bertani, Indena's technical director. "Moreover, it is based on a bus communication, thus reducing wiring and installation costs." In older systems, each instrument was wired directly to the host. The new bus, or fieldbus, uses a digital, multidrop communication link among intelligent measurement and control devices. The modular architecture uses fieldbus technology to create a local area network for advanced process control and remote input/output.

The software installed, called DeltaV Batch and AMS, supplied by Emerson Process Management (Austin, TX), receives data over an open network based on the Foundation Fieldbus protocol. Software using this protocol, developed by the Fieldbus Foundation, can communicate with equipment from multiple suppliers.

Through the new system's asset management function, plant operators will monitor equipment wear and tear. As

The top of a reactor vessel at the Indena plant.

the field instruments in the oncology line, which includes reactors and chromatography columns, perform their processing functions, they also measure various indicators of instrument health. Plant operators receive that data at central controls and use it to diagnose problems and schedule maintenance. The software can also be used to reproduce device calibration certificates, document test scheme changes, and report system administrator events.

Andrea Piotti, head of technical purchasing for the Settala site, believes that it is essential for systems to manage instrumentation assets as well as control batch processes. "It is clear that for companies to be competitive in the future they will have to adopt a total-plant vision and architecture that supports both the process control aspect and instrumentation maintenance," he said.

Bertani says the company plans to install a similar system when it opens a new department in Settala in the second quarter of 2004. Indena is one of the largest FDA-approved manufacturers of the oncology treatment paclitaxel, which is primarily used to treat ovarian and breast cancer. Indena Research also has recently isolated a new anticancer active substance called IDN 5109. This active pharmaceutical ingredient is obtained by means of semisynthesis starting from 14-β-hydroxybaccatin III (14-OH DAB), a molecule extracted from leaves of the *Taxus* genus. 14-OH DAB can originate a series of derivatives with cytotoxic activity. In March 2000, Indena signed an agreement with Bayer to supply the German company with the active ingredient, which may have a better anticancer profile than other taxanes currently available such as paclitaxel and docetaxel.

Laura Bush

Studies Support GCC for Pharma Use

Manufacturers hoping to meet the rise in consumer demand for all-natural therapies and dietary supplements are taking interest in newly available high-purity grades of ground calcium carbonate (GCC). Long considered by formulators as second best in purity, yet still more cost efficient compared with precipitated calcium carbonate (PCC), pharma-grade GCC has already been incorporated in several products. Calcium carbonate is predominantly used as the active ingredient in antacids but is also used as an excipient in solid dosage forms such as buffered aspirins. Raw materials suppliers are taking interest as the $50 million-per-year calcium carbonate–sourcing industry continues to face tough economic challenges.

A balance of purity and cost

The appeal of GCC comes as no surprise to ingredient maker J.M. Huber Corp. The company claims a 10–20% price differential between PCC and high-purity GCC. For products containing 96–98% calcium carbonate, the switch to GCC can mean a cost savings of as much as 50%. Most important, notes Michael Tarquini, PhD, the new-product leader of food and nutrition at J.M. Huber Corp. (Havre de Grace, MD), is that formulators no longer have to compromise purity for cost. In particular, the company has released data from independent-laboratory studies that compared the purity and lead levels of its grades of GCC with those of a leading PCC grade, a GCC grade from another manufacturer, and a J.T. Baker analytical standard (see Table I).

Conducted using USP protocol, the study revealed purity levels of GCC assays as high as 99.9% and levels of acid insolubles lower than 0.01%. According to the company, these values exceed US, European, and Japanese pharmacopeia purity standards. Especially interesting, notes Tarquini, is the 88-ppb lead-content level, which is well below the industry-adopted 125-ppb threshold. That standard was set as a result of the 1997 California Proposition 65 class-action lawsuit that stipulated a requirement of less than 0.5 μg of lead based on a calcium supplement or antacid dosage supplying 1000 mg of elemental calcium. According to Tarquini, "Leading USP-grade PCCs then available typically contained less than 50-ppb lead while their then-available GCC counterparts had trouble consistently complying with the Proposition 65 lead standard. At the time, the PCC products did indeed offer a very attractive lead 'purity cushion.'"

Today, however, Huber uses a new, highly pure GCC source. "It's not that we're doing anything to the substance," explains Tarquini, "rather, there are no contaminants in the source to begin with. We're mining material that has very high purity in the natural state. It comes out of the ground intrinsically highly pure and low in lead, which qualifies it as a truly natural product."

Granulation–tableting benefits

In addition to cost savings and the opportunity to advertise their products as "all natural" or "organic," manufacturers using GCC are reporting a number of processing advantages over PCC. "We have customers that work with both materials," says Tarquini, "and one of the things we're hearing is that the

Table I: Analytical results of GCC versus PCC grades.*

	Leading GCC	Leading PCC	HuberCal 850 Elite	Analytical standard
% Acid insolubles	0.09	0.09	<0.01	0.05
%Mg and alkali salts	0.51	0.47	0.31	0.91
ppb Pb	159	40	88	278
Assay (%)	99.4	97.2	99.9	99.1

*Study conducted at West Coast Analytical Laboratory, Santa Fe Springs, CA. Results provided by Huber Engineered Materials.

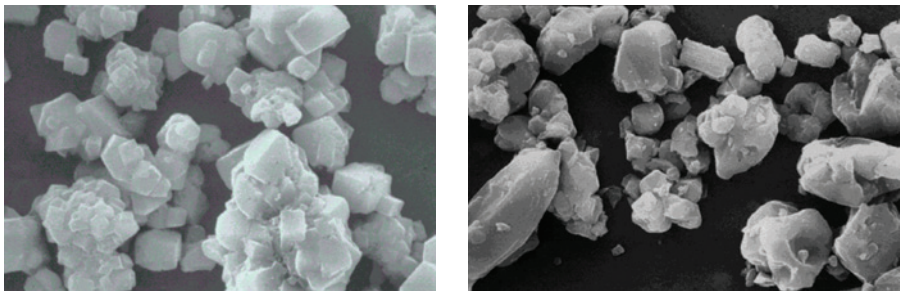

Figure 1: These photomicrographs of (left) 4.5-μm PCC and (right) 6-μm GCC particles show sharp, jagged edges on PCC and rounded edges on GCC. The sharp edges may abrade mixers and tableting dies and may contaminate product in the process. Because GCC particles are also softer than PCC particles, abrasivity is further reduced.

natural product GCC, including our new material, is intrinsically less abrasive than precipitated calcium carbonate. That means any type of equipment will see less wear, especially in tableting, where there is notably less wear on punches."

To support this claim, the company released the results of a study comparing the abrasiveness of a PCC grade and that of several GCC grades (see Table II). Conducted according to the Einleher method (Huber Standard Evaluation Method 2.122), the process involved the exposure of a Fourdrinier wire screen to the action of an abrasive suspension for a given period of time. The weight loss of the screen was then measured. "The results for two different leading PCC products and HuberCal GCC samples that varied only in particle size probably demonstrate the point most clearly," notes Tarquini. At both the 15- and 4.5-μm size, the abrasivity values differed by more than 2:1.

Table II: Einleher abrasion test.

Sample	mg loss/100 k revolutions
PCC A	14.48
GCC grade #1[a]	6.526
GCC grade #2[b]	9.620
PCC B	24.984
GCC grade #3[c]	13.007
GCC grade #4[d]	16.221

[a]HuberCAL 850, [b]HuberCAL 250, [c]HuberCAL 500, [d]HuberCAL 150

Scanning electron microscopy also shows a notable difference (see Figure 1). "Any type of mine stone has an inherent softness or hardness associated with it. In the case of precipitated forms, you're dealing with a crystal, it tends to be fairly abrasive," explains Tarquini. It is this abrasiveness that damages granulating and tableting equipment.

Patient preference

All other data aside, of particular importance to consumers are the results of a texture-analysis study conducted according to ASTM Manual 26 by 21st Sensory Inc. (Bartlesville, OK). A third-party manufacturer made tablets containing PCC and the company's GCC, and the blind samples were evaluated over a two-day period in regard to mouth feel. "When compared with similar or comparable-sized materials made of PCC, the GCC tablets had a 'less gritty' mouthfeel when the tablets were chewed and had less grit residual," says Tarquini.

Huber hopes that the qualitative and quantitative data will strengthen manufacturers' interest in GCC as a natural alternative to PCC for pharmaceutical products. The company recently announced the expansion of its tableting applications laboratory, a $500,000 investment and the first in the silica industry, for tableting at pilot-plant scale and for tablet characterization for excipient applications. The industry as a whole is already taking steps to revise much of the regulatory aspects of excipients, particulary in the efforts to harmonize excipient monographs. Interestingly, calcium carbonate is one of ten excipients currently under active discussion for harmonization.

Maribel Rios

Fast-Track Development Effort Pits Ribosome Expertise Against Growing Antibiotic Resistance

A round of funding is fueling fast-lane antibiotic discovery and development at Rib-X (pronounced rye'-bex) Pharmaceuticals Inc., a bioscience company formed in 2000 to address the problem of resistance to commonly used antibiotics. The company plans to replace existing antibiotics with new small-molecule drugs that work by inhibiting ribosomal targets.

"Our focus now is on bringing products to clinic," says Susan Froshauer, PhD, Rib-X's president and chief executive. "We are building a pipeline of clinical candidates for target markets." Among them are the markets for hospital-acquired and community-acquired infections.

The latest funding—$51 million in May—is pegged for additional research and development spending, specifically to drive efforts in building that pipeline and advancing compounds into clinical trials.

On the development front, work now centers on the selection of contract research organizations and on ensuring, as much as possible, that development efforts lead to candidate success in clinical trials. "We're setting up timelines, making sure that the kinds of drugs we have in mind are reasonable to synthesize to try to manage cost to manufacture," says Froshauer. "We are examining pharmacokinetic data that is driving us to safe and efficacious candidates. We are approaching the trigger point to scale up manufacturing."

Leading that effort is Scott Hopkins, MD, the company's vice-president of clinical development. Hopkins was most recently with Pfizer, where he had global responsibility for the clinical develop-

ment of such anti-infective agents as Zithromax, Diflucan, and Trovan.

"We are now looking for experienced regulatory people with anti-infective backgrounds," says Froshauer.

The target of common antibiotics is the bacterial ribosome, which is made up of a large and a small subunit. Many antibiotics cure disease by selectively inhibiting the protein-synthesizing activity of the large subunit while leaving human ribosomes alone. Over the years, however, many bacteria have become resistant to these agents.

Rib-X targets the large subunit, known as 50S. The company has an exclusive license for the high-resolution ribosome structure that was determined in 2000 by two of the company's founders, Thomas Steitz, PhD, and Peter Moore, PhD, both of Yale University. The company also has exclusive access to structure-based drug design software developed by company cofounder William Jorgensen, PhD, also of Yale.

As Steitz and his colleagues discovered in their research, the ribosome takes genetic information in the form of messenger RNA and converts it into protein. The researchers found that antibiotics that interact with the ribosome bind primarily to RNA, and not to protein, validating RNA as a drug target. Scientists can use this information to improve antibiotics that are already known to bind to the large subunit or to design new ones.

The detailed three-dimensional chemical and physical understanding of how drugs bind to the ribosome lies at the heart of structure-based drug design. The design software uses X-ray structures of antibiotic complexes and computer-aided design to guide the synthesis of chemical matter.

Froshauer anticipates the start of the company's first Phase I study in the second half of 2004. Labs have been opened just 18 months. "We're setting the hurdles high and hoping candidate attrition happens early in the preclinical development process. We're trying to fail before the clinic whenever possible," she says, "to avoid the costly late-stage failures that have recently accompanied some other forms of therapeutics, notably monoclonal antibodies."

George Miller

Cardinal Health Offers New Dermatological Delivery Technology

Scientists at Cardinal Health (Somerset, NJ) have manufactured a dermatological delivery technology that makes the delivery of active drug molecules onto and into the skin safer and more effective. Dubbed DelPouch, the single-use, sanitary dispensing system ensures that patients use the correct dose of the active ingredient without the risk of contamination.

Before DelPouch, a consumer had to define the correct dose of a topical medicine and touch the drug to apply it. Because correct dosage and cleanliness are two important factors in providing an effective medication, the delivery technology of DelPouch may replace existing methods. The foil pouch is filled with an accurate dose of a lotion, cream, or ointment. By squeezing the

foil pouch, the user releases the contents onto an attached applicator that is applied directly onto the treatment area. The applicator's surface can be either soft or coarse, depending on the content and the content's need. The system is then discarded after one use. The drug is not exposed to contaminants and is delivered to the skin in a safe manner.

According to David Wood, general manager of the topical technologies business unit at Cardinal Health, a need exists for a unit-dose pharmaceutical delivery product, and DelPouch is unique to other dermatological delivery technologies because "it allows patients to more accurately deliver the same size dose every time."

Characteristics and advantages

Currently, DelPouch is available in two sizes. One is a 0.8-g fill for a 0.5-g application, and the other is a 1.3-g fill for a 1.0-g application. The size of the dose depends on what the industry's demand is for topical products.

The fact that DelPouch is a single-use system also reduces the risk of contamination. Most topical drugs are applied with a patient's fingers. With DelPouch, the treatment area is only physically touched by the foam pad, which is discarded after use.

According to Rajiv Mathur, vice-president of skin care at Cardinal Health, DelPouch is ideal for drugs that are air-sensitive or light-sensitive (such as tretinoin or metronidazole). The delivery system also reduces any cross-contamination.

Manufacturing

Manufactured at Cardinal Health's facility in Humacao, Puerto Rico, DelPouch can be produced in an in-line process on commercial machines at the rate of 180 pouches per minute for a 0.5- or 1.0-g pouch fill.

According to Mathur, the heat-sealing system is a very important factor in the manufacturing process. Two pieces of foil film are sealed together using pressure and heat. Then, a foam applicator is heat-sealed on top. The exposure to heat strengthens the pouch, thereby ensuring that it will not tear when the consumer squeezes the pouch in the dispensing process.

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Outlook

According to a recent study by the Freedonia Group (Cleveland, OH), the demand for pouches in the United States is expected to climb nearly 7% annually, reaching $4.6 billion by 2006. In units, the demand is predicted to climb to 79 billion by 2006, up from 62 billion in 2001.

Cardinal Health plans to continue to work with vendors and pharmaceutical partners to adhere to the specifications that the industry demands. DelPouch will hit markets in June 2003, and according to Wood, Cardinal Health is predicting volumes of 50 million pouches in its first year and expecting extensive growth thereafter.

Doreen Coppola

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he says. "There are a lot of reasons right now to conduct research on the manufacture of antibodies to improve the process."

Donna Ambrosino, MD, director of MBL and professor of pediatrics at UMMS, agrees that manufacturing to scale is much easier if a cell line produces greater quantities of antibody, which is a part of process development. "Manufacturing monoclonal antibodies is always a matter of how much you can make and how fast," she notes. "As more of these antibodies are available, manufacturing becomes easier as we learn more about these products."

Ambrosino adds that manufacturing to scale is of course contingent upon manufacturing capacity. To make more antibodies, a company can use larger reactors or more reactor runs. MBL, a licensed FDA manufacturer, is expanding its own manufacturing capacity by building a $100-million facility that will be dedicated to monoclonal antibody manufacturing and aseptic filling. If the SARS market becomes too large for MBL's facility, Ambrosino says the MBL–Medarex partnership will have to assess its manufacturing options such as joining with other collaborators, outsourcing, or licensing out the formulation.

Lonberg expects that the cost of biologics manufacturing will come down in the future. "The industry has done a remarkable job in the past five years to develop high-yield processes that are bringing down the price of antibodies. I anticipate that about ten years from now the prices will be much lower because of technology development."

MBL is conducting the main portion of the research in its facilities using Medarex's UltiMAb technology, which consists of transgenic mice that have been engineered to create human antibodies.

Ronelle Russell