

New Delivery System to Administer Insulin Orally

BioSante Pharmaceuticals (Lincolnshire, IL) has developed a delivery system based on calcium phosphate to administer an oral form of insulin called Capic. The formulation has shown positive results in preclinical testing and promises an alternative to insulin injections.

The oral formulation of insulin and the new technology system were developed at BioSante Pharmaceutical's research center in Smyrna, Georgia. Scientists created the formulation by aggregating caseins, the principle protein of milk, around a proprietary formulation of the polymer polyethylene glycol

2–3% of the drug. "The casein doesn't degrade in acid; it protects the protein—the insulin," Bell said. The casein coating protects the insulin as it passes through the stomach and into the small intestine. The casein may also provide muco-adhesive properties that allow the drug to remain concentrated at the site of absorption, which results in slower, longer-lasting transport into the bloodstream. The calcium phosphate also reduces acid indigestion.

The idea to develop Capic stemmed from a simple notion. "The stomach can degrade active insulin," said Bell. "All [our] formulations can overcome normal acid degradation in the stomach."

Studies in mice showed that insulin administered through the new system was effective in reducing and maintaining blood glucose levels. According to Tulin Morcol, PhD, associate director of drug delivery and related technologies for BioSante, "Pharmacokinetic analysis indicated that Capic significantly increased the half-life and mean resistance time of the insulin. Furthermore, insulin in Capic form was eliminated from the body significantly slower than insulin in solution," Morcol said.

A single dose of Capic was administered directly into the stomachs of fasted diabetic mice whose blood glucose levels were monitored for 12 hours following the treatment to assess the hypoglycemic effect. When administered into the stomach, Capic rapidly reduced blood glucose levels by 80% within the first hour of treatment, and reduced glucose levels were maintained throughout the

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Colloid Gold Nanoparticles Deliver Cancer-Fighting Drugs

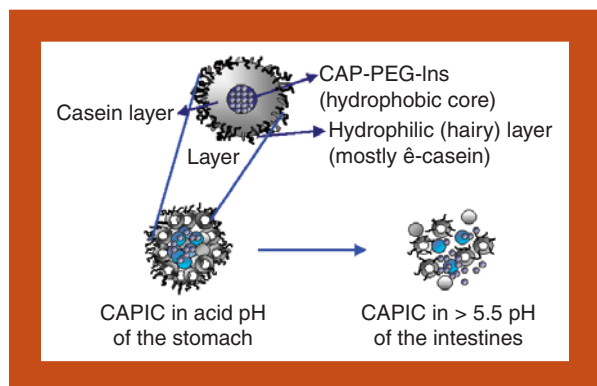
Colloid gold nanoparticles are currently being developed as a possible drug delivery technology to fight cancerous solid tumors. CytImmune Sciences, Inc. (College Park, MD) is partnering with Octo-Plus (Leiden, the Netherlands) to use colloid gold as a means to deliver the anticancer protein, tumor necrosis factor (TNF), for which they hope to begin Phase I clinical trials in December 2003.

Although TNF has a significant therapeutic potential for killing cancer, the amount of TNF that patients require has never been delivered successfully without eliciting negative side effects such as hypotension and in some cases complete organ failure resulting in death. However, when coupled with colloid gold (a combination of gold chloride and sodium citrate), beneficial amounts of TNF have been delivered safely in animal models, according to CytImmune's research.

CytImmune's scientists stumbled upon this use for colloid gold while experimenting with it to develop a different technology. "We found that we could eliminate the toxicity of biologically active agents by coupling them with colloid gold," says Lawrence Tamarkin, PhD, president and CEO of CytImmune. "We then realized that colloid gold had a larger potential than we first recognized. But the question remained, how do we harness this potential?"

The answer to his question evolved over eight years of developing colloid gold as a drug delivery technology. Because TNF binds to the surface of colloid gold, CytImmune's first formulation was to saturate the surface of col-

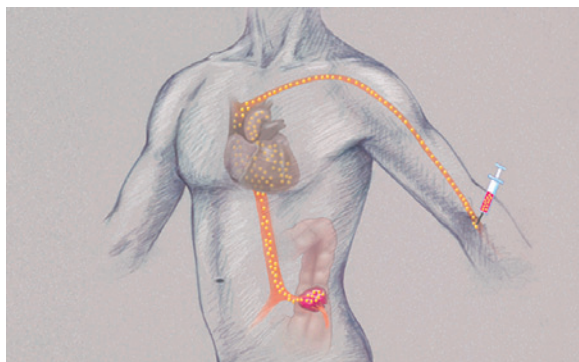
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In the Capic formulation, a layer of casein protects the insulin from degrading in the acid environment of the stomach.

(PEG) and insulin. The formulation, Capic, is created through nanoparticle technology, using microscopic particles of calcium phosphate, a natural compound found in teeth and bones.

According to Steve Bell, PhD, vice-president of R&D at BioSante Pharmaceuticals, each of the components that make up Capic plays a specific and unique role in the formulation. "The combination of the components is what makes the delivery system more effective than an injection," he explained. Casein, in particular, is one of the key components of the formulation and makes up



Colloid gold nanoparticles deliver cytotoxins to tumors.

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loid gold nanoparticles with TNF and inject it into mice. Although researchers were pleased that they could deliver a large amount of TNF to the mice without any noticeable side effects, they were troubled that they didn't see a significant antitumor response. After opening up the animals, the scientists found that the livers and spleens of the mice were black with aggregated colloid gold particles. Tamarkin explains, "Although we were able to give more TNF, we weren't able to improve its bioactivity because it was taken out of circulation by the organs and never reached the tumor."

Researchers then attempted the traditional approaches of masking the particles with materials such as blocked copolymers and forms of polyethylene glycol (PEG), all of which failed. Finally, scientists placed linear pieces of PEG in between TNF molecules, which were bound to the edges of the circular colloid gold nanoparticles. The linear pieces of PEG, placed like spokes in a wheel, became hydrated with water

when they came in contact with blood, causing the entire particle to become engulfed in water, which resulted in a surprising effect. "Once the particle is surrounded by water, it becomes a stealth particle," says Tamarkin. "The immune system thinks it's part of the body, and it can travel around the body without being trapped by these organs."

CytImmune uses colloid gold particles that are typically 25 nanometers in size, which is small enough to pass through holes (approximately 100 nm) in the blood vessels that surround a tumor. In healthy organs, spaces between blood vessels are only 5 nm, so colloid gold particles are able to pass into a tumor but are too large to enter any organs. Once the particle passes into the tumor, the TNF is immediately available for biological activity. From the 200–300 TNF molecules around each particle, one molecule acts as the anchor, attaching to cell-surface TNF receptors in and around the tumor, allowing the other TNF molecules to exert their anticancer action.

From the research conducted with animal models, CytImmune's scientists found that they can deliver 10 times more TNF to tumors with the colloid gold technology than before. Also, no long-term negative effects from using colloid gold have been noted thus far. Because only trace amounts are used for

drug delivery, the possible toxicity of colloid gold is difficult to determine. Scientists believe that the colloid gold nanoparticles are filtered through the kidneys after the active agent is delivered to the tumor, so no threat exists of the particles building up in the body over time.

Colloid gold has been used since the 1930s as a treatment for rheumatoid arthritis, but this development marks the first time that it has been applied as a drug delivery technology, which is now patented in the United States and Europe. Although it could have different applications in the future, CytImmune plans to focus on the use of this technology for cancer drug delivery. "It's not tomorrow's technology—it's today's," states Tamarkin. "Cancer is, in our minds, a national plague. We believe this can be an effective therapy for today."

TNF only represents the first of several drugs that can be delivered with colloid gold. CytImmune is also conducting studies with Virginia Polytechnic Institute (Blacksburg, VA) to bind Taxol (paclitaxel), a small-molecule therapeutic, to colloid gold. In this formulation, TNF will be the targeting molecule to home in on the tumor, and Taxol will be the therapeutic payload.

Collaborating with CytImmune, OctoPlus will produce the final product of TNF coupled with colloid gold nanoparticles for clinical trials to begin in December. If the clinical trials are successful, a product should be available to the marketplace by 2007.

Ronelle Russell

Asthma Product Enters the Elusive Medical Food Market

For companies like Pilot Therapeutics (Charleston, SC), the medical food category provides an attractive alternative to the minimally regulated dietary supplement and the heavily regulated pharmaceutical drug industry. A medical food is defined in the 1988 amendments to the Orphan Drug Act of 1983 as "a food which is formulated to be consumed or

administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."

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Airozin, a new asthma treatment classified as a medical food.

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Airozin, Pilot's all-natural formulation for asthma patients, was a perfect medical food candidate. "We had a product that met the underlying need of asthmatics and we felt the product needed to be differentiated from the



Floyd Ski Chilton

multitude of nutritional products," says Pilot's CEO Floyd Ski Chilton, PhD.

Medical foods, which are neither prescription nor over-the-counter, must meet a few requirements to enter the marketplace. As Chilton notes, "the toughest requirement is showing that the medical food meets an underlying dietary need in a disease population." In Airozin's case, its formulation provides natural fatty acids that reduce the production of leukotrienes, substances known to cause asthma attacks.

Airozin, which is currently being test-marketed in select areas of North and South Carolina, is composed of concentrated gamma-linolenic acid from borage seed oil and eicosapentaenoic acid from marine oil. The end result is an orally ingested, orange-cream-flavored liquid emulsion, packaged in individual doses, for the dietary management of asthma.

For much of their existence, medical foods have received little attention. FDA's current regulation does not extend much beyond the 1988 definition. Claims of medical foods must be based upon scientific standards translated into some type of evidenced safety and efficacy, a characteristic that Chilton says made the medical food category desirable. "Medical foods must undergo much more rigorous regulatory standards than dietary supplements," he notes. Even though clinical trials aren't necessary for medical foods, Airozin went through five clinical trials, including one at Quintiles (Lenexa, KS) and a pharmacokinetics investigation of pediatric subjects. Chilton did comment on the advantages of medical food claims. "Medical foods can mention human disease, unlike the structure-function claims of dietary supplements," he said. Airozin's label does include a disclaimer

that the product is not a replacement for any asthma medication.

Medical foods also must be used under the supervision of a physician, a fact that should be clearly stated on the product's label. Another FDA-dictated labeling guideline requires that a statement be made that the product is intended to manage a specific medical disorder or condition.

Premarket approval for medical foods is not required, but there have been cases where products claiming to be medical foods were eventually reclassified by FDA.

As the medical food industry grows, FDA has turned its attention to strengthening regulation because of safety and quality control issues associated with manufacturing as well as fraudulent claims not backed by sound scientific principles. Currently, medical foods are exempt from the nutrition labeling, health claims, and nutrient content claims required of most foods, and their claims do not need to meet specific standards. Without nutrition labeling or premarket approval, there is no certainty that products are suitably formulated for the targeted patient population.

In November 1996, FDA published an advanced notice of proposed rulemaking that contains extensive commentary about how best to regulate medical foods. FDA cannot comment on the medical food regulations currently under consideration, but the proposed rulemaking raises issues such as the need for a stronger scientific substantiation for claims, a need for a clearer definition of what constitutes a medical food, stricter and clearer labeling requirements, and a specific product safety policy.

FDA has yet to publish the proposed rules, but the effects of any future FDA regulations on the medical food industry do not worry Chilton. "It is already incredibly important for products that fit into the medical food category to undergo rigorous safety trials." In the meantime, Pilot Therapeutics gears up for Airozin's 2004 national launch.

Felicia Pride

Manufacturing Role Evolves with Pharmaceutical Business

Pharmaceutical manufacturing professionals find themselves at a crossroads.

As the business around them contracts and folds through mergers and acquisitions, and as executives focus on R&D pipelines to ensure a future for their companies, manufacturing can appear almost mundane by contrast.

"The days of the pharmaceutical company being manufacturing-driven are over," says Kate McCormick, PhD, a pharmaceutical manufacturing consultant. "Many companies no longer see manufacturing as a core competency, but merely as an activity that must be carried out efficiently."

Yet at the same time, regulators are imposing ever-larger financial penalties for CGMP noncompliance (most notably the \$500 million penalty for Schering-Plough last year) and ultimately have the authority to close down a facility. As a result, executives ignore manufacturing at their peril.

"Executives should view [manufacturing] as an investment, not an expense," says McCormick. "Validation is required to demonstrate compliance, but validation can have other benefits—equipment efficiency, for example—that are internal to a company."

McCormick is the author of *Manufacturing in the Global Pharmaceuticals Industry: Key Drivers, Company Strategies and Regulations*, published recently by Urch Publishing, a UK-based pharmaceutical business information provider. McCormick's 20 years of pharmaceutical manufacturing experience began in line management and progressed to international production for a multinational pharmaceutical company.

Though industry-wide cost cutting has squeezed investment in manufacturing, the manufacturing function remains

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important to a pharmaceutical company's viability. As a result, pharmaceutical professionals having manufacturing expertise "have become more valuable," says McCormick. "If manufacturing is the 'poor relative' within a company, fewer people want to become expert so there are fewer people who specialize."

"The question—why should we invest [in manufacturing]?—should be balanced by an understanding of the implications of not making that investment," she said, adding that in an industry as highly regulated and quality critical as the drug sector, the ability of manufacturing to deliver consistent quality is a prerequisite for remaining in business. She likens pharmaceutical industry manufacturing today to manufacturing as a whole several years ago when the total quality management paradigm reigned. The idea now, she says, is that manufacturing quality is a given across the pharmaceutical industry and no longer stands as a competitive differentiator.

This may be one factor in the rise of contract organizations as a manufacturing option within the pharmaceutical industry. "Contract manufacturing is a growing trend," says McCormick. "In the past it was a tactical decision rather

than a strategic one. Now strategic outsourcing of manufacturing is more common, particularly when the quality is high and the cost is reasonable."

This trend can be seen in the operations of contract manufacturers such as MOVA Pharmaceutical Corp. (Caguas, Puerto Rico). MOVA specializes in formulation scale-up to manufacturing for existing products and line extensions. Like all contractors, MOVA must also supply regulatory support and stability testing.

According to José E. Casellas, vice-president for corporate business development, MOVA caters to four distinct customers. First is "Big Pharma," for whom MOVA has become "a component of their sourcing strategy." Big Pharma accounts for about 70% of MOVA's business today.

Second is "Medium Pharma"—those companies that are acquiring products from Big Pharma and those that have niche products. "We have manufacturing expertise," says Casellas, "and because of it we become part of their supply chain. Many of these companies don't want to develop that capability."

Rounding out the customer types are those supplying generic products that are looking for capacity, and "virtual

companies"—those with a strong R&D pipeline who need manufacturing expertise in the latter stages of commercial development.

With Big Pharma representing so much of MOVA's business, the contractor has some very demanding customers. "We have to manufacture much quicker but at the same high levels of quality" that Big Pharma companies provide in their own manufacturing operations. As such, MOVA's equipment is geared to its customers' needs and particular processes. "It's not about having equipment," says Casellas, "but having the necessary equipment training to provide the required process."

MOVA's 20% investment in manufacturing quality and training systems is about on par with that of Big Pharma, according to Keith Symmers, vice-president at Best Practices LLC (Chapel Hill, NC).

Symmers and his team found in a benchmarking study that leading companies have about one person in a quality function for every five manufacturing employees. Researchers interviewed vice-presidents, directors, and managers involved in quality and plant functions at companies such as Abbott Labs, Eli Lilly, and GlaxoSmithKline in its study entitled "The Quality Function: Structures, Staffing and Execution," published late last year.

"There are so many ways to do it well, so many ways to screw it up," says Symmers about manufacturing. He notes that FDA provides little latitude in meeting the commitments required in a new drug application. Yet manufacturers "are innovating and making changes while still meeting those commitments."

Symmers estimates that the benchmarked Big Pharma companies outsource less than 5% of their manufacturing, mainly for new and specialized products. He expects this percentage to rise in coming years and that the percentage of employees dedicated to manufacturing at big pharma companies will shrink as more manufacturing is outsourced and as the sales and marketing functions grow within these companies.

Table 1: Advantages and disadvantages of options for pharmaceutical manufacturing.

Option	Advantages	Disadvantages
In-house	Guarantees quality control High workforce interaction Simpler registration process	Significant ongoing investment Product differentiation expensive
Partnerships	Share expertise Reduce cost Pre-empt copy products	Relationship management difficult Trust in partners
Joint Venture	May need a local presence Overcome cultural barriers Less investment required	Loosening of product control Relationship management difficult Split management
Contracting out	First step into new market Much less capital investment Local manufacturing presence	Loss of product quality control Requires regular auditing Best suited to older products
Outsourcing	Reduce capital investment Reduce time to market Increase flexibility Use existing technology expertise	Loss of control Need extensive reporting system Good teamwork needed
Licensing out	Revenue with limited investment Extend life of older products	Almost total loss of product quality control Brand name may suffer

Source: Urlich Publishing

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Contract Proteomics Laboratory Targets Drug Discovery and Development

Charles River Proteomic Services Inc. (Worcester, MA), recently opened its fee-for-service research laboratory to aid



clients in identifying proteins related to specific diseases and conditions and developing them into treatments. The joint venture is 80% owned by Charles River Laboratories and 20% owned by Proteome Systems Ltd. It operates from the same facility that houses Charles River's Discovery and Development Services.

The 10,000-ft² laboratory houses PSL's ProteomIQ technology platform and a complement of IT infrastructure for the separation and characterization of proteins. The Proteome platform, based on 2-D gel separation, includes tools, automation, mass spectrometry, and bioinformatics for high-throughput proteomics research. ICAT and multi-dimensional chromatography capabilities are also available to clients from their offices via the Internet.

Charles River Proteomic Services President James A. Jersey, PhD, expects those clients to include Big Pharma companies branching into the data-intensive field of proteomics as well as small and large biotech companies. Such companies can undertake discovery and

development projects using the contract services, he says. Among the services are sample preparation and separation; image analysis, spot excision, and digestion; sample analysis by mass spectrometry; and bioinformatics.

The outsourcing of drug discovery and development functions is growing rapidly and now accounts for a \$2-billion industry worldwide, according to Kalorama Information, a life sciences research arm of MarketResearch.com. Kalorama projects the contract services field to continue to grow at a brisk pace, approaching \$6 billion by 2007, according to its new study, *Outsourcing in Drug Discovery*.

George Miller

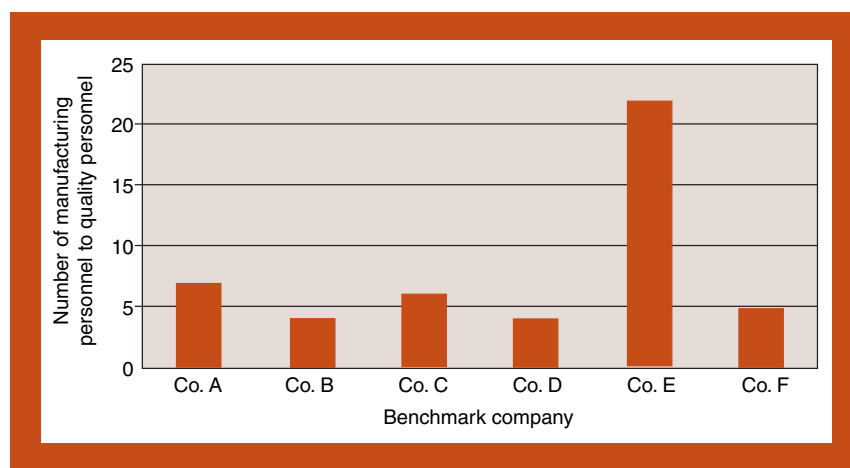
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12-hour blood-sampling period. In contrast, the same amount of insulin alone reduced glucose levels by only 20% in the first hour and by 35% within five hours, after which time blood glucose increased sharply to baseline.

In fed diabetic mice, administration of Capic into the stomach reduced glucose levels by approximately 50% within the first three hours, with a return to control levels within six hours. In contrast, the same dose of insulin alone had no significant effect on glucose levels.

BioSante Pharmaceuticals plans to conduct further studies with the insulin formulation and continue to develop CAP-Oral, the technology behind this formulation, for the oral delivery of other therapeutic proteins that currently must be injected. "CAP-Oral is a platform delivery system that can benefit a wide range of product applications in the areas of oncology, allergy, or any other therapeutic delivery protein drugs," said Bell.

Doreen Coppola



Manufacturing and quality personnel. Most surveyed companies have about one person in a quality function for every five manufacturing employees.

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Best Practices finds that the companies that do invest in manufacturing excellence share particular ideas about structure, staffing, and execution. The key is well-trained, knowledgeable teams of personnel, according to the report. Among its findings is that training and certification programs pay dividends by keeping employees up to date on QA/QC developments. In addition,

companies must switch from a reactive approach to one that seeks to identify quality problems before they occur.

"Building an effective auditing function requires going beyond merely identifying issues with batches before they leave the plant. Although this is a crucial task, successful auditing functions will also uncover larger systemic problems and monitor improvement efforts."

George Miller