

## **Drug Discovery News**

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### **Outsourcing Feature:**

### **CROs, CMOs Ride Outsourcing Growth**

By Lloyd Dunlap

By definition, outsourcing involves farming out work under contract to outside sources – contract research organizations (CROs) and contract manufacturers (CMOs) – who do it, and “it” can be almost anything or everything. Much as in the fable of the seven blind men who variously describe the elephant as a snake (the trunk), a tree (the leg), etc., the role of CROs depends very much on who you’re speaking to.

The category sprang up in the ‘80s as a job-shop industry handling spill-over capacity, according to Joseph Herring, chairman and CEO of Covance Inc. (Princeton, NJ), one of the industry’s five behemoths that constitute 45% of all CRO revenues. A decade later, the landscape changed dramatically with the emergence of thousands of biotechs who lacked internal development capabilities. Over the past several years, the race has been “to take nascent companies in a nascent industry into leadership positions,” Mr. Herring says. As far as he knows, all pharmas and biotechs use CROs. Covance, he believes, has larger capabilities than even most large pharmas.

“We have a core strategy,” Herring relates, “which is to take time and cost out of drug development in order to bring the miracles of medicine to market sooner.” To do this, his company provides scientific and regulatory capabilities that are fast, efficient and easy to use. The productivity model based on consistent throughput halves the time from first-in-animal to first-in-man. “That’s how we get clients, keep them, increase our margins and can afford to invest \$150 to \$200 million per year,” Herring adds.

Among the industry-wide trends Joe Herring sees are:

- More outsourcing by large pharmas, shifting the current client mix which is 60% specialty pharma/biotech and 40% large pharma and accelerating growth for the CRO industry.
- Increased in-licensing of drugs not in a company’s area of discovery development expertise to fill pipelines.
- Continuing movement of clinical trials from “clogged” areas in the U.S. and Western Europe to Eastern Europe, Asia and Latin America.
- Establishing facilities in China, Singapore and elsewhere to help open new markets for U.S. pharma. Short-term, a second benefit is accessing a labor market that is 50% or more less costly.
- Toxicology and drug discovery support work will remain mostly in the U.S. and Western Europe.

Ken Getz, senior fellow at the Tufts Center for the Study of Drug Development at

Tufts University, echoes Joe Herring's conclusion that strategic partnering is a growing phenomenon. According to Tufts Center data, pharma who do manage CROs as collaborative partners to complement their core capabilities enjoy consistent speed and cost advantages. In a study published in January 2006, which purported to be the "first comprehensive quantitative analysis of the overall impact of outsourcing on drug development performance and capacity," the center found that drug sponsors who are more extensive users of CROs "complete projects faster, most notably during the study close-out period, while maintaining quality comparable to submissions involving minimal use of CROs."

Over the two years since the study was published, Getz continues to see rapid growth in CRO usage. Counter to what might be expected in most markets, the fastest growth is occurring among "mega CROs," Getz notes. Other trends Getz sees are rapid proliferation in the number of companies sponsoring one or more clinical studies – according to InformaHealth, the number has shot up from 900 companies to 1,600 actively in clinical trials – and "a really notable decline in internal capacity to handle clinical trials in-house." Finally, Getz expects the industry to see the continuing globalization of clinical trials, with half going abroad today – mostly to Central and Eastern Europe and China.

Philosophically, Ken Getz notes that "It's not a clean observation to say our productivity is declining," because safety and efficacy are more difficult to establish with chronic disease, which is a growing area of R&D emphasis. If 60-year-old, \$1.5 billion Covance is one of the 800-pound gorillas in the CRO space, Alisa Wright's BioConvergence LLC (Bloomington, IN) is close to the other end of the continuum. Launched in 2004 to provide development, supply chain, materials management and consulting services, the company is 80 percent owned by Ms. Wright and two female partners, employs 32 and has 60 primarily biotech clients centered in the U.S., Canada and Europe.

"The drug development time line is too long and costs too much money," Wright notes. Wherever possible, BioConvergence uses technology to effect savings. For example, lab personnel use electronic notebooks and templates to save time and enhance data integrity. "Right now," Ms. Wright says, "it feels like our industry is like a lake undergoing inversion. Large companies are seeking out niche players. Small pharma and biotech want one-stop shopping but wind up not as high on the totem pole. Large pharma have gone the one-stop shopping route and been disappointed with efficiency and cost. To often, they outsource but demand the partner do things exactly as they were done internally, which doesn't make much sense."

On another hot-button issue, Ms. Wright says her company has won business back from China and India. "For product development," she says, "both large and small customers who had pilot programs in India and China now work with BioConvergence," with innovation being at the top of their lists. "From discovery

to commercialization, our industry has lots of room for improvement,” she notes. “The question is, ‘How do we get better together?’”

BioConvergence may be successfully bucking the “China Syndrome,” but MPI Research (Mattawan, MI) is embracing it, having recently announced a joint venture with Shanghai Medicilon. Bill Harrison, president and COO, says a team of MPI experts will relocate to Shanghai and form a GLP advisory board to oversee the U.S. FDA GLP compliance process, which he expects to be in place by mid-2009. “Our challenge is managing growth,” Mr. Harrison states, which has been a heady 30% CAGR over the past 10 years. MPI provides a comprehensive range of preclinical drug discovery and development research. Privately held, it doesn’t reveal revenues, but employs 1,600 people, which should peg annual revenues in the \$250 million range.

“We think there’s work out there for everyone,” Mr. Harrison say. “and we’re not convinced the whole industry will move offshore. When the wall came down, Eastern Europe was the big concern. Now, API, chemistry services and clinical trials are top candidates for offshore sourcing. Our plan is to outgrow the marketplace, grow share, be sure we have capacity available and produce results at a fair price.”

Another CRO which seems to sense, in Alisa Wright’s words, that “the lake is at a mixing point,” is Celsis International plc. John Daniels, vice president and general manager of Chicago-based Celsis Analytical Services believes the pharma model is becoming more “convoluted.” He notes, as an example that AstraZeneca has been quoted as wanted to get totally out of manufacturing.

Other pharmas are spinning off older products, which strains the resources of companies who take them on and creates opportunities for CROs and CMOs. Celsis’ analytical services bring value to clients, Daniel observes, with very quick turnaround to support manufacturing and get to market faster. “We know that pharma CEOs are driving the outsourcing bandwagon. We’re trying to stay on top of this to liaise with them and meet their needs,” he states. As Celsis continues to expand, Daniels foresees the need for offshore labs. “But ADMETox is so specialized, we can probably serve the market from here,” he notes.

Another CRO that has emerged from the shadows of big pharmas problems is Midwest BioResearch, LLC (Skokie, IL), which opened its door in October 2003 after Pfizer acquired Pharmacia and closed its Illinois-based operations. President Michael Schlosser and others from Pharmacia’s preclinical department bought equipment from Pfizer and started the business that now numbers 45 staffers. The CRO has doubled staff and revenues every year, Dr. Schlosser notes, and has clients in the U.S., Europe and Israel where the biotech industry is taking off. “We focus on drug disposition and toxicology,” Schlosser says, with a special interest in protein therapeutics and antibody assays required for regulatory and IND. “The path for protein therapeutics through discovery and

development is more predictable than with small molecules,” Schlosser says, “and toxicity is primarily antibody oriented.” In his view, diversity is the trend in the industry, with one-stop shops hard to find in practice. At best, he notes, multiple sites are necessary even within a “one-stop” shop.

Whether big pharma is, in Joe Herring’s word, suffering a “constriction,” Daniel’s “convolution, or Wright’s “inversion,” none of the major pharmaceutical companies we contacted chose to express their views on outsourcing. Endocyte (West Lafayette, IN), a three-year old biopharmaceutical company with several folate-receptor targeting oncology drugs in Phase I and Phase II clinical trials, did however. “We will always be dependent on CMOs,” says Al Ritter, vice president CMC. “We develop the lead and manufacturing protocol for GMP manufacturing of API materials. When we go out with a RFP, we understand the attributes and the variables of the process. It’s been ‘road tested.’ We don’t go out and say ‘we need this in a month.’ We plan out six months to a year.”

Endocyte works with relatively small quantities of cytotoxic materials so to outsource the company looks globally for the best scientific fit, and currently works with CMOs in Europe, China and India. “Timely communication is very important to us,” Ritter states, “whether the news is good or bad. In our three year history, there’s never been an issue we haven’t resolved and we’ve never been late delivering a drug product.”

Dr. Stephen Munk, president and CEO of CMO Ash Stevens (Detroit, MI) contends that there are problems with compliance in China. “We’re experienced in chemical development and the chemical aspects of the regulatory process. Being U.S.-based is now considered an advantage where it wasn’t five years ago,” he states. His company specializes in custom syntheses per cGMP manufacturing, with lot sizes ranging from 10 mg to kilos. Most of the work is performed under government contract for material to be used in toxicological and early clinical studies. Though a 45-year old company, Ash Stevens became active in contract research just over 10 years go. “No one wants to invest in specialized manufacturing infrastructure that may only be used 5-10% of the time.” Of the fewer than 100 NMEs since January 2003, Dr. Munk notes with more than a little pride, Ash Stevens has been responsible for producing three.

Finally, in an example of “way out-sourcing,” WaferGen Biosystems (Fremont, CA), is in the process of establishing a Malaysian subsidiary to support development and commercialization of its SmartChip real-time PCR system. Why Malaysia? WaferGen’s chairman and CEO Alnoor Shivji explains it this way: A Malaysian friend based in the U.S. told him of a new focus on biotech in her home country. A December 2006 fact-finding mission to determine the country’s capabilities in biotech and high-tech manufacturing was a pleasant surprise. “The SmartChip requires hi-tech for the instrument and scientific expertise for the primers,” he notes. He visited genome centers at a number of universities and discussed his project with professors and leaders of institutes. The government,

he adds, is providing “various very attractive incentives,” including \$2-\$2.5 million in matching funding. Shivji plans to have five to 10 people on board at his subsidiary in Kulim Hi-Tech Park in Kedah Malaysia initially, and grow it to 50-100 over time. He will be outsourcing some chemistry and biology, as well as eventual production to CMO Pentamaster Corp. Berhad in Penang.