naquality.com

Pharmaceutical Formulation & Quality

MAY/JUNE 1999
$10.00

For Product Development and Quality Professionals

INTEGRATED EFFORT:
THE ROLE OF CONTRACT LABS IN DRUG DEVELOPMENT AND TESTING

LIMS: THE PROOF IS IN THE PLANNING

PRESERVATIVE TESTING WITH SPIRAL PLATING

A LOOK AT *PHARMANEX*
V. SHALALA

manufacturing process control." But these successes with LIMS don't come right out of the box, they come through planning, expertise and work.

McDuffie, whose company helps in all aspects of LIMS implementation, from workflow analysis to writing custom code for instrument and software links, says the secret to success with LIMS is having a good and balanced working relationship between lab people and information technology (IT) people. "Our company is about half lab people and half computer people," he says. "Successful configuration and customization means putting lab and IT together. People run into trouble where one half is missing."

The integration of LIMS into the lab and into the larger world of enterprise computing might also be becoming less of a burden on LIMS vendors if new software such as BusinessBus from Compaq is a success. These programs serve as dedicated translators between business applications, relieving LIMS vendors from the need to burden their own programs with scores of translators. This way LIMS can go back to concentrating on the lab, leaving other jobs to other specialized packages integrated in the framework.

McDuffie expects LIMS to become ever more flexible, with less effort required in implementation, but sees no "straight out of the box" LIMS in the future. "As long as lab people believe they have to do things in their own special way, configuration and customization will be an issue. There is no standard lab, so there will be no standard LIMS."

Resources

To acquire The Analytical Consumer *or participate in one of its industry surveys, visit world.std.com/~jjordan/ on the Internet, or phone Jo Rita Jordan in Carlisle, MA at 508-369-9079.*

FDA maintains a page on CFR 21 Part 11 at www.fda.gov/cder/esig/index.htm

PDA's website is www.pda.org

IEEE's website is www.ieee.org

The Validation Institute puts on "The LIMS Conference" annually, concentrating specifically on the pharmaceutical industry. It can be contacted at 888-670-8200.

The Internet site for the LIMS e-mail list, a valuable resource covering the gamut of LIMS-related issues, is www.users.fast.net/~millers/lims.html. The list has recently come back online after a short hiatus. The list FAQ is a valuable resource in itself.

KMI/Parexel
Belmont, MA
800-458-9920
www.kminc.com
Circle 260 on the RS Card

Taratec Development Corporation
Newark, DE
302-368-4040
www.taratec.com
Circle 261 on the RS Card

INTEGRATI

Contract testing laboratories are an important part of many companies' product development and testing programs–programs that are becoming extremely complex on one hand and pinched by time and monetary pressures on the other. Outsourcing has been a common way of addressing the contradictory demands made on today's pharmaceutical manufacturers, but contract labs can do a lot more than pick up slack.

by Bruce Flickinger

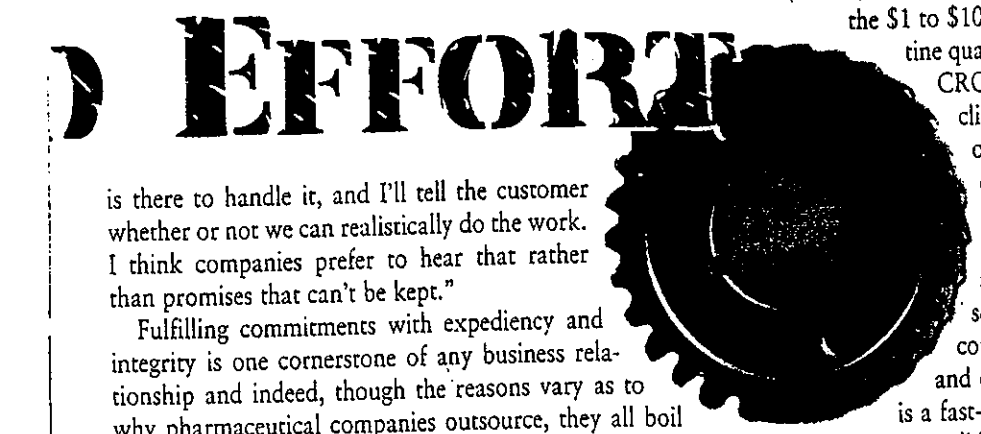
The contract laboratory business is, in many ways, a microcosm of the American dream: identify a need in the market that is not being served, acquire some funding and some first-rate people, start up the business with a few customers gained through word of mouth or long-standing friendships, do what's necessary to retain the business, and then continue to grow from there.

Such a scenario happens quite frequently in today's market for outsourced research and analytical services. Certainly, there are larger players, many of which have funded growth through public stock offerings, and are beginning to consolidate for better economies of scale, much like the companies they serve. But a host of small and mid-size players is in the field, and by all accounts there is enough business to keep everyone sated for at least several years into the next century.

ical chemistry for both manufacturing companies and contract laboratories, tells a story typical of many of these smaller players. He formed Quality Chemical Laboratories last August with two partners, Yousry Sayed, Ph. D. and Thomas Wright III. The three spent six months writing SOPs, ordering equipment and putting it through its calibration and IQ/OQ/PQ paces. A staff of five was hired and the doors openeed for business this past January. In the few months since then, the staff has grown to 15.

"Good service at a fair price is what we saw missing from the contract lab industry," says Meeks, who is Vice President and Chief Operating Officer of the Wilmington, NC, company. "It's been my experience that, at times, pharmaceutical companies are at the mercy of the contract lab. So they'll settle for less service simply because they have no other options. Let's face it, they wouldn't outsource if they could do it themselves. But many contract labs overcommit–they take on the work when they can't really do it–which compromises service and turnaround times to the client."

Though some might construe having too much work as a good problem, Meeks says it's important to understand that "you can't always say yes. We keep track of capacities–I know each chemist's work capacity, and based on these numbers, I know how many monographs a particular group can release in a week. I can look on the computer at any time and know the status of all work in the lab, so when a request comes in I know whether the capacity



is there to handle it, and I'll tell the customer whether or not we can realistically do the work. I think companies prefer to hear that rather than promises that can't be kept."

Fulfilling commitments with expediency and integrity is one cornerstone of any business relationship and indeed, though the reasons vary as to why pharmaceutical companies outsource, they all boil down to good business. One commonly cited driver is the number of blockbuster drugs whose patents are expiring–"2003 and 2005 are going to be big years," says one source–which means two things: the innovator drug companies will need to refill their pipelines while the generic companies will need to hustle to get their own versions to market. And as the process of drug discovery, development, testing and manufacture has become significantly more complex and specialized on one hand, and pinched by unavoidable economic realities on the other, contract testing organizations, along with providers of various technologies and services, play important roles in mitigating the clash between these two market forces.

So while there is opportunity aplenty, "It all comes down to quality," Meeks says. "Quality work is what gives you a chance at getting business, and then service is how you distinguish yourself and keep the business."

THE BIG THREE

Quality is joined by turnaround time and service to form the indispensable triad for a contract laboratory working in the pharmaceutical industry. To this some will add price, though pharmaceutical companies will frown upon any suggestion that they shop for analytical services based on cost.

"There's a lot of overhead in quality assurance, so you need to be wary about bargain basement prices because costs are almost always reduced by cutting quality," says Herbert Prince, Ph.D., Research Director with Gibraltar Laboratories of Fairfield, NJ. "The squeeze on contract labs is to get it done quickly, inexpensively and correctly, a configuration of expectations that is hard to meet. We feel that the most immutable of these is getting it right."

There is certainly enough business to be gained. Varying numbers are presented to characterize the pharmaceutical contract lab market in the US; a common tally is that over $30 billion dollars are spent annually on pharmaceutical research and development–with roughly half of that on clinical trials–and about $3 billion of those R&D dollars are outsourced. About 50% of this business goes to 10 of the largest contract research organizations (CROs) and the remainder to several hundred labs and CROs in the $1 to $10 million sales range. Similar numbers for routine quality testing are more elusive, though given that CROs have done much to expand the capacity for clinical research, pressure to do more is exerted on the product testing and manufacturing end of the spectrum.

Gibraltar is a 30-year-old company offering microbiological, chemical and viral testing, *in vitro* and animal toxicology, environmental services and contamination control. Like many contract labs, it does both pre-clinical research and quality control. Rapid microbial identification is a fast-growing part of the business, Prince says, as is new facilities validation, providing an objective approach to validating air and water systems, personnel hygiene and other GMP functions.

"Quality encompasses two things: scientific integrity and compliance," Prince says. "The two are equally important. All data going through our lab is reviewed and approved by senior-level people. It's important that all documentation is reviewed, audited, archived and accessible to government and sponsor audits."

For larger contract organizations, such as Magellan Laboratories of Research Triangle Park, NC, quality is the watchword, particularly when doing work for multinational companies, whose data will support products being launched or distributed worldwide and will undergo that much more scrutiny. "Much of our business comes from top-tier major international companies who are looking to increase speed to market and outsource their major stability programs," says William E. Weiser, Ph.D., Director Analytical Chemistry and Pharmaceutical Synthesis with Magellan. "This includes line extensions and more complex, definitive NDA stability programs for new entities. For intermediate size companies, a major stability study would outstrip their capacity." Regardless of the client, "We make no distinctions in the quality of service. From our perspective, we don't know what the sponsor companies are using the data for, so we treat all requests as if they are being submitted to a regulatory authority."

BEATING THE CLOCK

After data integrity and quality of work, timeliness is critical. "We need to understand the timing issues that are driving our sponsors," Weiser says. "We can't work with everyone on the basis of, 'do my work first,' but timeliness can be an extremely important issue. In clinical trials, for example, if a lab is causing delay or po-

Integrated Effort

tential abandonment of the trials, then it is detrimental to the sponsor's business as well as the lab's."

Turnaround time is a big source of complaints for microbiological work. "We need to get results out to the client as quickly as possible, particularly when a material or product does not meet specifications and manufacturing needs to make a decision as to its disposition," says Bob Friedel, QA Manager with Perritt Laboratories of Hightstown, NJ. "But the chemistry department personnel think microbiological tests can be generated in the same time frame as a chemical test, such as gas chromatography. The problem is that you're dealing with living organisms that don't always abide by your schedule. As a result, its always been difficult to discuss microbiological issues with management."

Courtesy Quality Chemical Laboratories

> "I can check the status of all work in the lab at any time, so when a request comes in I know whether the capacity is there to handle it, and I'll tell the customer whether or not we can realistically do the work. I think companies prefer to hear that rather than promises that can't be kept."
>
> –Phil Meeks,
> Quality Chemical Laboratories

Friedel has also seen things from the other side, having come to Perritt after working as a microbiologist in OTC product development and preservation at Whitehall-Robins Healthcare. Perritt's primary businesses are microbiological testing of pharmaceuticals, cosmetics and toiletries, and testing of child-resistant package for a variety of industries. "We do a lot of routine, microbiological quality testing as well as developmental work," he says. "Our laboratory fulfills a function that many smaller companies cannot perform on their own. Also, many companies are downsizing, so they're concentrating on the things they do best and contracting out the excess, such as calibration and validation work."

Weiser and others feel that one way to speed up turnaround times is to reduce the hierarchy of departments or chains of command that clients have to negotiate. "We want to facilitate scientist-to-scientist communication," he says. "You don't want to have requests going through a customer service group, where data integrity and scientific interpretation can be lost."

Meeks concurs, and has organized his operations so that a dedicated group of chemists is responsible for an entire project, from the time samples arrive until the generation of final reports. Customer calls go directly to the team leader. "It's important to have good workflow systems. We have an automated computer system set up that does everything from sample log in and scheduling to report generation. It really streamlines our operations."

ACCOUNTING FOR DIFFERENT TASTES

The service part of the contractual equation is largely synonymous with communication. Sources contacted for this story were unanimous in saying that effective, two-way communication is what ensures a long-term relationship. The management of a contract relationship takes planning and control. The initial contract itself is very important; it is a verification of what the working relationship will involve. The contract must designate what quality control procedures are entailed, and set out other important performance metrics that must be monitored.

"The most important thing in developing and maintaining a relationship with a contract lab is to agree on everything up front," says Eric Gruff, Ph.D., Manager of Pharmaceutical Development at Agouron Pharmaceuticals, a 1,000-employee company in La Jolla, CA, specializing in the development of new drugs used in virology, oncology and ophthalmology. "This includes small details such as timelines for testing and reporting of data, requirements for training of new analysts, format of reports, notification of OOS or potential OOS situations, and when the lab needs to notify the sponsor that they need more reference standards. We have had problems when a contract lab bought 'equivalent' HPLC columns to save money and was unable to meet system suitability requirements for the assay."

Gruff's responsibilities include managing relationships with contract laboratories, ensuring compliance with corporate policies and governmental regulations, and overseeing the review and analysis of data from contract facilities. "We usually send stability testing to contractors, which includes development, registrational or post marketing studies on solid oral, nasal and parenteral dosage forms," he says. "Microbiological testing for release of components, APIs and drug products is always sent out, since we do not have the capability to perform those tests in house. The main reason we send out the physicochemical testing is because we don't have sufficient resources to meet the demand. We may have several strengths, presentations or packages for a particular product, which can lead to a large stability program, so we try to be intelligent about balancing the need for hands-on work with a new product with resource constraints."

While some are wont to paint the typical partnership between drug company and contract lab as a rosy, mutually beneficial partnership, Gruff sounds a common theme: "I would say that

the typical vendor relationship is still a 'client-vendor' one. It's very difficult to delegate or contract out certain responsibilities during drug development, and with FDA paying so much attention to GMP laboratories for PAIs, it's imperative that the sponsor ensure that a contractor is doing the same things that it is. Many contract labs have a generic set of SOPs to handle different procedures and situations, and they need to take these 'vanilla' documents and add sponsor-specific details to them to make them consistent with customer policies."

Friedel notes that "communication is not always on the level that it should be. The transfer of relevant microbiological information from clients, such as preservatives present in a formula, is not always iron clad. Some clients are hesitant to disclose information, so they don't give us the level of information we need to provide them with accurate microbiological test results."

Weiser says that with different projects from various clients occupying the lab, confidentiality is a concern along with particular methodologies or needs. "Our systems are designed to maintain rigorous separation and ensure clear distinctions between sponsors," he says. "There are no cross references to sponsors between projects or documentation. All data for individual sponsors are kept in notebooks specific to that study, with no two sponsors in the same notebook."

EXPERIENCE AND EXPERTISE

While contract labs have been important in picking up excess workload, some of the work performed by contract labs is esoteric and highly specialized. Tapping a particular expertise is one of the main reasons pharmaceutical companies look to outside help, particularly as so-called virtual companies now proliferate, and as scientists in small and large companies alike become increasingly specialized and limited to specific areas of research.

"Contract labs have extraordinary expertise because of the broad spectrum of activity we see," Prince says. "Drug companies often come to us to do something they don't know how to do or to do something they know but don't have facilities or resources for. Key staff members at contract labs tend to be experienced industry people, and they often have a deeper background than the people on the industry side. This is why good contract labs are so highly regarded. Our people are asking questions and solving problems, not just reading recipes."

"Having the right people is critical," Weiser concurs. "You need bright people with the desire to succeed and knowledge of both the industry and pharmaceutical chemistry. They need to be able to deal with multiple sponsors, methods and styles. So it's important to have a talented and sophisticated staff."

Areas where this technical expertise is sought include synthetic chemistry, development of compounds for biological screening, purity/degradant method development, characterization studies, and deformulation and preformulation studies. At Quality Chemical Laboratories for example, Meeks sees growing interest in areas such as synthesis and compound identification. "We can do small-scale custom bench synthesis, batches of 10 g or less, for developing reference standards for impurities and metabolites," he

INTEGRATED EFFORT

says. "A company might have an unknown impurity showing up in its stability testing and we offer the ability to synthesize it and identify it."

Other specialty services include deformulation, where a finished product is broken down into its component parts. Scientists are then able to tell exactly what is in it and develop methods to quantify everything in the matrix. "This is a particularly valuable capability for generic drug companies, whose formulators try to closely mimic innovator drugs largely through educated guesswork," Meeks says. Isolation and purification are also growing areas. "If a company has an impurity in one of its products at, say, .3%, and they don't have the time or capabilities to figure out what it is, we can find out what is causing the impurity through degradation studies, then identify it by collecting the impurity peak off an LC-MS and using techniques such as IR, NMR, MS or even crystal studies. This way the client knows what it is when the FDA asks them to identify it."

> "You need bright people with the desire to succeed, and who are able to deal with multiple sponsors, methods and styles. It's important to have a sophisticated staff."
>
> –William Weiser, Ph.D.,
> Magellan Laboratories

Courtesy Magellan Laboratories

THE HARDER THE AUDIT, THE BETTER

Audits by FDA inspectors are joined by client audits and self audits as the three types of inspections and performance evaluations that labs undergo continuously. Gruff and his colleagues perform on-site audits, and sometimes do a technical pre-audit evaluation before the QA department does the formal audit. "We return annually if there are no serious issues," Gruff says. "We try to have a long-term relationship with just a few contract labs, but this hasn't always been possible for a variety of reasons."

While clients visiting labs is common, Gruff believes that management personnel from contract labs should spend some time visiting their sponsors, "not just to have lunch and chat about all the new things that they're planning, but to go into the labs and see how the sponsor handles its testing programs. That would make things easier for both sides, because questions and issues could be quickly identified and resolved. Many times, a sponsor lab has a unique approach to testing or analyzing data, and they don't understand why the contract lab is doing it differently. A pharmaceutical company should find a lab that has a similar style or approach to testing, and one that is flexible with respect to doing things in a manner that is consistent with what the sponsor wants."

The staff at Magellan is no stranger to audits: last year about three customer audits occurred each business week. "Audits give us an outside perspective on our systems, so they are helpful," Weiser says. "Actually we learn the most from the challenging audits; we don't benefit as much from the easy ones."

"We encourage client audits, although they dont seem to happen as frequently as I think they should," Friedel says. "Auditors want to see some structure in our quality system, because the manufacturing companies are ultimately responsible for the results we generate. We are required to follow our own standard procedures as well as meet each clients guidelines/specifications. We need to be as good or better than they are."

This may sound straightforward enough, but it can be a difficult task for a contract lab to pull off, particularly because clientele in the pharmaceutical industry is saddled with a stiff regulatory and reputational liability, and fierce competitive pressures. For these companies to hand business over to an outside lab represents a measure of risk, a financial investment and a less than ideal circumstance. But outsourcing is an unavoidable reality of doing business: the world's largest companies do it, as do upstart virtual companies that have little more than office space and the ownership or licensing of a product or technology.

Certainly there are benefits of a progressive, well-managed sourcing strategy, notably improved capital and asset utilization for pharmaceutical companies. Companies need to ask themselves when it makes good business sense to partner with other companies that can do core competencies with better technology, more flexibility, better control and costs containment, while remaining secure. Pharmaceutical manufacturers need to look at the entire value chain, which includes research, product launch and marketing.

For the legions of laboratories and research organizations standing at the ready to assist in these endeavors, unassailable analytical capability and standards of quality assurance are what separate the labs that stay viable and profitable from those that do not. "Reputation is everything," Prince says. "If you lose a customer, you can always get them back or get another. But if you lose your reputation, you're in trouble. That's why it's most important to do the work right." PD

Gibraltar Laboratories Inc.
Fairfield, NJ
973-227-6882
www.gibraltarlabsinc.com
Circle 250 on the RS card

Magellan Laboratories Inc.
Research Triangle Park, NC
919-481-4855
www.magellanlabs.com.
Circle 251 on the RS card

Perrilt Laboratories Inc.
Hightstown, NJ
609-443-4848
www.perrittlab.com
Circle 252 on the RS card

Quality Chemical Laboratories
Wilmington, NC
910-796-3441
www.qualitychemlabs.com
Circle 253 on the RS card