BY DENISE MYSHKO

CROS and Preclinical Development

As lab budgets remain constricted, pharmaceutical and biotech labs are outsourcing preclinical and drug discovery services to CROs.

DR. PETER SMITH ■ *Millennium Pharmaceuticals*

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To create efficiency and offload the need to maintain staff, instruments, and consumables for irregularly scheduled projects and projects that extend beyond their scope, more labs are engaging CROs as outsourcing partners, according to a recent report by BioInformatics LLC.

Thomas Jones, Ph.D., senior director, toxicology and pathology, Eli Lilly and Company, believes it is likely that more and more of the preclinical studies conducted each year to support drug discovery and development will be managed by CROs.

"With this shift, CROs must accept greater responsibility in terms of product delivery," he says. "In addition to running studies and supplying data, they must emerge as the true experts in the study types and models they offer to their clients. It is essential they invest in the preclinical models and the technologies that will maximize the probability of success for the sponsor in the short term and drive adoption of improved approaches for compound development in the longer term. Accordingly, the optimal model is one that focuses on providing outcomes."

Dr. Jones says this necessitates a greater degree of expertise and ownership regarding the design, implementation, and interpretation of the study.

"For example, preclinical studies are often affected by findings that are not considered compound-related," he says. "These are often referred to as background findings. Nevertheless, without solid documentation of the nature and frequency of these findings, a sponsor may find itself in a regulatory quagmire upon submission of such data."

Dr. Jones says with many major CROs offering a full range of services in support of preclinical and clinical development, there is an opportunity to create a seamless flow of information and activities to accelerate the progression of a molecule into the clinic.

"This will require a different operating model where information and planning no longer ping-pong back and forth between the sponsor and CRO, but rather there is a process that is self-managed within the CRO with the opportunity for input and adjustments by the sponsor company," he says.

For smaller companies, outsourcing preclinical services to a CRO can be both economical and time-effective, say Peter Smith, Ph.D., senior VP, nonclinical development sciences at Millennium Pharmaceuticals Inc.: The Takeda Oncology Company.

"There are other advantages for smaller companies to associate themselves with a CRO, including gaining access to individuals who may have particular expertise that may be lacking in the sponsor organization," he says.

Dr. Smith says there are other advantages associated with CRO outsourcing, including: gaining access to a team of experienced drug-development experts across a broad range of compound structures and therapeutic targets; eliminating the fixed-costs associated with building a nonclinical organization; and removing the regulatory hurdle imposed by the conduct of in-house regulated (i.e. GLP) studies.

Dr. Jones says for CROs to better serve their clients they need to invest more in understanding the model systems they employ and have better information/knowledge management systems so that they can provide the appropriate insights needed for the interpretation of study outcomes.

"CROs also need to be able to place the appropriate context around all findings — those that are compound-related and those that are not," he adds. "As sponsor companies try to maximize their chances for success in development, there is a greater need for support of toxicology activities in discovery as well. These studies tend to be smaller in scale with very short cycle times to allow iterations within the chemical series. To establish the capabilities needed to better serve all phases of toxicology support, CROs must embrace these studies. This is not simply running the same studies non-GLP. The approach to support discovery studies needs to be flexible with respect to design and implementation, and there has to be a focus on the key learnings in order to select a candidate molecule for development."

Additionally, Dr. Smith says a CRO should be able to deliver the product on time, working with staff members on the project team who are expected to meet often very aggressive timelines while ensuring the delivery of high-quality data.

"Both of these depend on focus and having the assignment be the No. 1 priority for the involved individuals," he says. "For the highest priority projects, challenge the team to beat the benchmarks and reward them extraordinarily for extraordinary accomplishments. Project teams often strive to exceed expectations. Having a well-defined process and practice for all activities, empowering the project team, and streamlining the bureaucracy to enable fast executive management decisions are keys to success."

Preclinical Development: Best Practices

In terms of improving preclinical development, a lot of progress has been made, but there is still much more to accomplish, says Alain Stricker-Krongrad, Ph.D., chief scientific officer at Charles River.

"Major efforts must be made to accelerate the bench-to-clinic transition, as well as to implement de-risking strategies," he says. "The industry needs a paradigm-changing solution. The trend toward innovation is very strong. The trend toward increased drug attrition between and within therapeutic areas is building the case for the use of more innovative technologies and solutions."

Dr. Jones says the conduct of quality studies is at the top of the list of best practices for managing preclinical development timelines.

"This requires well-trained staff at both the CRO and sponsor companies who understand the complexities of orchestrating the design and conduct of a preclinical toxicology study, including how to adjust to the unexpected events that often accompany the initial detailed characterization of the toxicology profile of a new molecular entity," he says. "Mechanisms and processes to maintain communication and openly share information among all parties involved in a study is the key to maintaining its integrity."

Additionally, Dr. Jones says it is important to have an understanding of what is needed in the final product — a report that will satisfy worldwide regulatory authorities — and eliminate any non-value-added activities or steps that distract from the most efficient means of delivering that product.

Continuous improvement programs, such as Six Sigma, can be used to define the key study-related processes and maximize the efficiency of coordinating and completing those processes to support the regulatory submission.

"We have found that the application of focused efforts on the key, rate-limiting phases of the timeline to be a powerful tool for improving the timeline in preclinical development," Lilly's Dr. Jones says. "By avoiding the distraction associated with multitasking we have been able to define the true touch-times for key activities and thereby dramatically reduce cycle times."

A focused effort requires scheduling each critical task or activity and completing it from start to finish using only the necessary touch-time, Dr. Jones further explains. This operating paradigm requires an organizational commitment but can pay big dividends in terms of timeline management. ✦