ACHIEVING VALUE from Discovery and Preclinical Endeavors

Denise Myshko

Drug developers are looking to derive more value from their discovery and preclinical programs, as a way to increase the hit rate and advance candidates to clinical development that have less toxicity.

The need to increase value and productivity throughout the development process has never been more critical. R&D expenditure continued to drop in 2010 to an estimated three-year low of $68 billion, and drug success rates continue to show the declining trends of the past decade, according to the 2011 Pharmaceutical R&D Factbook compiled by CMR International. Additionally, the number of drugs entering Phase I trials fell 47%.

As a result, experts say the bar has been raised for preclinical studies because researchers now know much more about the mechanisms of disease.

"No longer are developers shooting into the dark hoping to hit a target of importance," says Ken Kramer, Ph.D., senior VP and medical director, Alpha & Omega Worldwide, part of The Core Nation. "Now, there is the ability to target particular points in a disease pathway and then engineer new drugs that will, hopefully, work well with few adverse events."

A critical part of the preclinical process is to identify compounds that may generate toxic effects in human patients," says Chris Parker, VP and chief commercial officer at Cellular Dynamics International.

"Unfortunately, toxicity testing has been handicapped by the availability, until recently, of cell-based tools that poorly reflect human biology," he says. "Such cell systems include primary cells from animals, tumor-generated immortal cell lines, and cells derived from human cadaveric tissue. Not surprisingly, unexpected toxicities emerge during clinical trials and, in some cases, following product launch. Considering the need for pharmaceutical companies to improve productivity of their drug discovery processes, tools that better recapitulate human biology will provide significant advantages and improve the drug discovery hit rate."

Dr. Kramer points out that this trend was first seen in the area of oncology, where compounds such as Herceptin changed the face of breast cancer treatment by providing patients with a targeted therapy.

"When it was discovered that breast cancer cells that expressed the HER2 receptor grew more aggressively, this provided an opportunity to develop targeted therapies," he says. "We anticipate that this trend will not only continue, but also expand as we learn more about biochemical and genetic pathways of disease."

Technology has advanced tremendously, and now genetic engineering and recombinant gene technology are capable of producing human proteins that have identical sequences to natural ones and work with high efficacy and safety, Dr. Kramer says.

"In the past, many disease states such as diabetes were treated with insulin derived from pigs," he says. "Yes, it worked well, but the goal has always been to replace a missing or malfunctioning human protein with a human protein. There are now nearly 100 recombinant proteins in clinical use today ranging from those used to treat bleeding disorders to disease-modifying therapies for treating multiple sclerosis. For other diseases, such as cystic fibrosis, the best we could once offer patients was supportive or palliative care. But by gaining an understanding of the genetic contributions to various diseases, now medications can be created that can help even more patients with serious, once life-threatening disorders."

Christine Copeman, scientific director at Charles River, says other technologies that enhance the drug development process in the clinic include: applications that assist in the exchange of microscopic findings on studies and allow the informal exchange of ideas; use of telemetry systems that allow incorporation of cardiovascular endpoints, where appropriate, within a main safety assessment study, to permit concomitant evaluations of possible cardiovascular effects following repeat administration; and use of imaging capabilities to reduce the number of animals required for a study and to monitor progression of change over time.

Challenges of Preclinical Development

Philip Toleikis, Ph.D., president and CEO of Sernova, says it is important to carefully assess the amount of preclinical work required to sufficiently derisk a program before heading into clinical trials.

"There is a fine balance between spending too much time and money on preclinical evaluation and ensuring a program is derisked sufficiently to bring the product forward quickly for testing in the clinic," he says.

CHRIS PARKER ▪ *Cellular Dynamics*

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"Sometimes the cost of large animal model proof-of-concept studies can be more expensive than an initial clinical study and the animal model may not be reflective of how the product may work in humans. So, in a sense continuing to spend money and time on preclinical work can actually increase the risk to a program."

Another challenge, according to Jennifer Brice, life-sciences global program manager at Frost & Sullivan, is making sure the development program is in line with what the FDA would look for to support the planned Phase I trials.

"This requires close interaction with the FDA starting at the preclinical stage," she says.

Outsourcing: Discovery and Preclinical

The global drug discovery outsourcing market is expected to be valued at $16.21 billion by 2015, up from $8.30 billion in 2010, according to a Visiongain report, Drug Discovery Outsourcing: World Market 2011-2021. A key market driver for outsourcing is the reduced costs of performing functions such as custom synthesis, target validation, and high-throughput screening, the report finds.

GBI Research estimates that the global preclinical outsourcing market was valued at $3.8 billion in 2009 and is expected to grow at a CAGR of 11.2% to reach $7.9 billion by 2016.

Key growth drivers in the preclinical outsourcing market include increasing R&D expenditures, cost advantages in Asian countries with respect to preclinical R&D, and laboratory animal requirements.

Ms. Copeman of Charles River says the experience of a CRO can be a valuable asset to any sponsor whether in preclinical or clinical development.

"At the preclinical level, CROs can provide keen insight into developing strategic programs based on their knowledge base with a wide range of compounds evaluated and ensure the programs are focused on regulatory requirements," she says. "They provide cost-effective study designs and specialized resources and can also facilitate communication with the FDA and global regulatory agencies. By identifying issues early, CROs help ensure that sponsors perform just the appropriate studies needed to expedite the drug development process. Sponsors further benefit by saving resources, which can be channeled to new program starts."

With drastic budget challenges and a more stringent regulatory environment, drug companies are searching for creative ways to design preclinical studies so as to maximize expectations for patient outcomes, says Christina Fleming, Ph.D., executive VP of scientific and medical affairs, at Advanced Clinical.

"Although translational medicine has not been a large focus for many service providers in the past, CROs have started to explore the implementation of early-phase development programs, which focus on the prediction of patient safety and exposure-response outcomes through extrapolation of preclinical findings," Dr. Fleming says. "By investing in the development of such programs, CROs are better equipped to partner with sponsor companies, especially smaller or start-up organizations that do not have the in-house knowledge. With the ability of service providers to offer guidance and processes for forecasting preclinical-to-clinical findings, contract research organizations are becoming better equipped to provide basic research-design strategy expertise and, as a result, help to optimize clinical trial outcomes while preserving clinical research costs."

Dr. Toleikis says he has found CROs to be very useful for the standard pharmacokinetic, toxicology, and biocompatibility testing of products.

"Where they have fallen short is when an animal model must be transferred to the CRO to conduct specific testing," he says. "There often isn't the expertise to efficiently and accurately make the transfer. Therefore, under certain circumstances it might be useful for CROs to hire experts as consultants to help with the transfer of specific animal models to the CRO facility."

Best Practices in Preclinical

As the number of moving parts within each preclinical study increases, the ability to track these projects and their deliverables is becoming increasingly more difficult, says Pamela Shaver-Walker, director of global reporting services at Charles River.

"As a result, it is critical to have a knowledgeable project coordinator to ensure the IND program's deadlines and deliverables are met," she says. "This includes weekly conference calls with monitors and subject matter experts, along with their CRO principal investigator and study director counterparts, to discuss the molecule's development status and address any issues, so timelines are not impacted."

In addition, more sponsors are making the shift to strategic relationships, Ms. Shaver-Walker says.

"A strategic model offers both the sponsor and the CRO numerous benefits, including a relationship at multiple levels," she says. "Strategic relationships often have governance committees and comprise of key individuals from the operations team, up to the executive level, which enables issues to be easily addressed with support from management teams to ensure that programs stay on track. The strategic model creates deeper relationships on both sides, which results in better service, consistent communication, and stronger commitments. These partnerships allow the sponsor and CRO team to better integrate sponsor objectives, become part of the sponsor's team through knowledge sharing, and establish a good level of trust for a successful outcome."

Dr. Toleikis suggests instead of trying to guess what preclinical work regulatory authorities will want to see, companies should focus on the regulatory requirements as well as what they would want to know about their product to be comfortable testing it in humans.

"The company knows the product best and most often what studies should be conducted," he says. "Once a plan is developed it is impor-

DR. PHILIP TOLEIKIS ▪ *Sernova*

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tant to share the information with the regulatory authorities to reflect on the plan and determine what else might be needed. This approach provides the company with greater confidence when engaging with the regulatory authorities and the level of collaboration is much higher. The process also tends to be more focused and efficient from a timeline perspective." PV

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