BY DENISE MYSHKO

Preclinical Development: LINKING THE LAB TO HUMAN TRIALS

Most product candidates often fail in the preclinical stage. High-quality toxicology studies and companies' ability to adapt to unexpected events are critical to managing preclinical timelines.

The challenge of pharmaceutical discovery and development as a whole is that a large number of conditions need to be met in order for a single molecular entity to successfully reach the market, says Thomas Jones, Ph.D., senior director, toxicology and pathology, Eli Lilly and Company.

"The molecule needs to have the appropriate specificity and potency against the intended targets, it needs the right biopharmaceutical and ADME characteristics to be absorbed and reach the site of action, it needs to be able to be manufactured, and of course it needs to be safe and effective," he says.

Jean-Jacques Garaud, M.D., global head, pharmaceutical research and early development, Roche, says in the past 20 years, there has been too much focus on speed and timelines.

"I prefer an approach that favors quality outcomes versus timelines, one that leverages the new tools from the life-sciences revolution and fully integrates them into the development process," he says. "This is more likely to take us away from the attrition-based model into a biology-centered model, thereby significantly decreasing attrition rates."

Dr. Jones says portfolio decisions made in this phase are focused entirely on preclinical study-defined risks, and there is no clinical benefit to counterbalance these decisions.

"While preclinical phase failure fits the often overused mantra 'fail fast,' it can, in some instances, represent a huge opportunity loss," he says. "With the right risk management plan, a greater number of preclinical phase compounds could be moved into clinical development, providing greater context around benefit as well as risk and insight into the role of the target in human disease."

Recognizing the significance of toxicology at the interface between discovery — the identification of clinical candidate molecules — and development — the test of the clinical hypothesis and satisfying global registration requirements — defines two key opportunities for the preclinical safety organization, Dr. Jones says.

"The first is to effectively partner with the discovery organization, with chemistry and biology being the primary customers, to develop compound screening and selection paradigms that incorporate safety considerations to improve the probability that any resulting candidates achieve first human dose," he says. "In the discovery phase, the goal is to discharge as much risk as reasonable before selecting the final candidates. Then, once a candidate is resourced for development, the focus and the customer base of the preclinical safety organization shifts. Medical and regulatory become the key customers and partners to effectively manage issues allowing safe entry into the clinic."

FAST FACT

PRECLINICAL TESTING CAN TAKE FROM ONE TO FIVE YEARS, AND MUST PROVIDE INFORMATION ABOUT THE PHARMACEUTICAL COMPOSITION OF THE DRUG, ITS SAFETY, HOW THE DRUG WILL BE FORMULATED AND MANUFACTURED, AND HOW IT WILL BE ADMINISTERED TO THE FIRST HUMAN SUBJECTS.

Source: PPD

Preclinical: Challenges

Experts say there are many obstacles that may impede the development process at the preclinical stage, including selecting the best preclinical animal models; identifying biomarkers for immune response, preclinical rationales to support the targeted patient population, and preclinical rationales to support clinical go/no go (GNG) decisions; standardizing immunogenicity testing; navigating changing regulatory requirements; and analyzing postmarketing surveillance and epidemiology.

But Peter Smith, Ph.D., senior VP, nonclinical development sciences at Millennium Pharmaceuticals Inc.: The Takeda Oncology Company, says the greatest challenge facing preclinical science continues to be the need to provide accurate predictions of human toxicities and pharmacokinetic properties.

DR. THOMAS JONES ■ *Lilly*

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"Several published reviews indicate that failure rates based on toxicology in the clinic continue to be high, and clearly the complexity of extrapolation of results from animal toxicology studies to patients continues to be a significant challenge," he says. "On the other hand, better progress has been made in predicting pharmacokinetic behavior, largely because these evaluations better facilitate the use of human enzymes and tissues that somewhat facilitate the extrapolation step."

Dr. Jones agrees, adding that relevance of toxicology in the process of drug development is made clear in that preclinical safety findings continue to drive the largest proportion of compound failure across the industry.

"This fact is often overlooked because about 80% of industrywide, toxicology-driven attrition occurs in the preclinical phase before the large clinical development dollars are spent," he explains. "This means that the largest portion of toxicology-driven compound failure occurs before candidates ever reach a human volunteer or patient."

Unforeseen drug toxicities and patient responses have companies reexamining the processes driving preclinical development in drug discovery, Dr. Smith says.

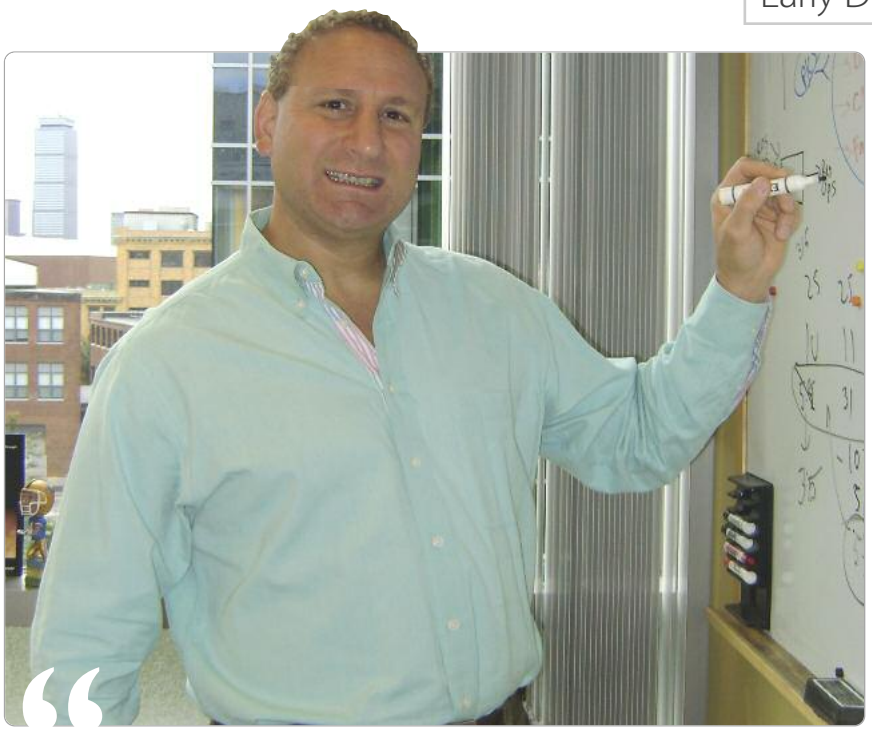
"This is leading to a variety of novel methods — imaging technology, early assessment of combination effects, nanotechnology, and modeling and simulation-based approaches — that may minimize compound toxicity, optimize target identification, and improve lead identification," he says. "The Critical Path Initiative, sponsored by FDA and PhRMA, is targeting ways to better predict potential drug toxicities, as well as efficacy to sharpen decision-making on drug candidates."

Dr. Smith says as a result there is a closer partnership between research and preclinical scientists and the incorporation of technologies, such as target visualization and pharmacology screening, earlier into the global safety assessment for agents with particular mechanisms of action.

"We were the first company to routinely leverage pharmacodynamic markers in GLP toxicology studies," he says. "Identifying and using pharmacodynamic markers is fairly common today in pharmacology testing. To our knowledge, there is one other company today that employs PD markers in toxicology studies, but I expect that all major companies will quickly move to this strategy."

Dr. Smith says for oncology, the greatest challenge is in balancing the potential benefit of the cancer agent against the all too frequent adverse effects in normal tissues linked with the intended pharmacology.

"There are several tactics available to mitigate this potential risk," he says. "For example, tumor targeting of the drug candidate versus plasma or nontumoral tissue load is one approach based on pharmacokinetics, but this is often difficult to design for in small molecules. On the other hand, with the increasing interest in antibody drug conjugates (ADCs), the targeting of specific tumor surface markers is possible with greater specific distribution of the therapeutic to the intended target cell. Today, we are focusing more and more on cancer treatment modalities that minimally affect normal tissues."



DR. PETER SMITH ■ *Millennium Pharmaceuticals*

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Preclinical: Technologies

Dr. Jones says predictive and screening technologies include a wide range of approaches ranging from in silico models, capable of predicting biological responses based on chemical structure, to those technologies that can be applied to in vitro and/or short-term in vivo models with the goal of predicting longer-term outcomes.

"Sponsor companies are investing and applying these technologies to varying degrees using independent training sets — compounds for which there are known outcome data," he says. "Imaging, another area where there is increasing interest, has the potential to transform our approach to preclinical study monitoring the progression and/or reversibility of compound effects."

Dr. Jones says knowledge management has become increasingly important in preclinical development.

"Each new preclinical toxicology study generates a great deal of information," he says. "Limitations in our ability to manage study-related information in a way that makes it accessible for mining and analyses across multiple studies restricts our ability to transform this information into knowledge. With the volume of preclinical toxicology data being generated in the CRO environment, it is imperative that these data are captured and managed in a way that makes them accessible to knowledge management approaches."

Dr. Jones says the key is to understand what preclinical information is needed to drive decision-making.

"New biomarkers could play an important role in drug development by enhancing the characterization of the preclinical safety profile," he says. "Even greater value can be envisioned in those cases where the utility of a novel biomarker can be translated into the clinic."

Alain Stricker-Krongrad, Ph.D., chief scientific officer at Charles River, says new imaging technologies will take on larger roles in preclinical development.

"The measurement of molecules with imaging tools will increase, probably to the point where a direct assessment of nucleic acid levels will be made in living organisms," he says. ✦

MICRODOSING: A COMPELLING ADVANTAGE

Microdosing or Phase 0 clinical testing has been gaining acceptance and might become an imperative phase of the drug development process in the years to come. The emergence of niche capability providers in preclinical testing and technology dependence is also expected to result in numerous partnerships and alliances, fuelling growth opportunities in this sector.

"The compelling advantages of microdosing present it as a potential remedy for big pharma's maladies regarding declining returns from investments in drug development," notes Frost & Sullivan Senior Research Analyst V. Sriram.

Source: Frost & Sullivan.
For more information, visit pharma.frost.com.

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