NEW MODELS for Early Development

Denise Myshko

Biopharmaceutical companies are starting to implement new approaches to early clinical studies as a way to reduce costs and failure of drug candidates.

The number of drugs entering Phase I fell 47% and the number of drugs entering Phase II trials fell 53%, according to 2011 Pharmaceutical R&D Factbook complied by CMR International.

Industry experts say there is a trend toward conducting fewer, more complex early-phase studies that often include patients. As a result, more innovative study designs and specialized skill sets, as well as access to patients, are required to address this growing study complexity.

There is clearly a big drive among biopharmaceutical companies to implement new and innovative approaches to minimize their early-phase development times and cost, while at the same time significantly reduce the failure rate of their products during later-stage trials, says Sy Pretorius, M.D., corporate VP and worldwide head of early phase at Parexel International.

"Merging elements of what was traditionally deemed Phase I with Phase II into a complex proof-of-concept (POC) study is definitely increasing in interest as a way to gain the stated efficiencies," he says. "These complex POC studies are primarily designed to find signals of product efficacy in the target patient population as early as possible. The focus is to provide more efficient delivery of better, faster go/no-go decisions from first-in-human (FIH) through proof of concept."

Dr. Pretorius says studies in healthy volunteers will remain an integral part of drug development in the foreseeable future.

"But there is a focus more on patient studies, as well as hybrid patient-healthy volunteer studies, as demand increases in this regard," he says. "To achieve development goals, access to numerous patient populations is needed for early-phase studies, including proof-of-concept studies."

There is a need to include more and more early indicators of safety, proof of concept, and efficacy in early development, says Pierre Geoffroy, M.D., VP, early phase, at INC Research.

FAST FACT

PHASE I OUTSOURCING ROSE FROM 35% IN 2008 TO 58% IN 2011.

Source: Cutting Edge Information.

"These assessments are highly relevant to sponsors for later decision-making, and for smaller biotech companies, financing for later stages of development," he says. "Super protocols are one way to incorporate multiple objectives under one study. This allows saving some front-end costs and timelines, but good planning capabilities and scientific/medical expertise are needed so that subject safety and study practicality are not sacrificed."

Dr. Geoffroy says the FDA's emphasis on risk-benefit means that potential issues should be addressed early on, to eliminate unsuitable candidates or focus development efforts on indications where risk-benefit ratios are more favorable.

"For example, many sponsors now include time-matched ECGs right from early single- and multiple-ascending dose studies, which along with PK/PD analyses, can provide invaluable data for later stages of development," he says.

Challenges of Early Development

Dr. Cyril Clarke, VP of translational medicine at ICON, says everyone in the industry needs to think about predicting effectiveness as early as possible.

"Our mindset should be one of potential responder population enrichment as early as possible in development as an active strategy rather than a reactive mindset of retrospective data mining," he says. "Producing packages that take payer reimbursement decision-making into consideration early in the development process is gaining in importance.

DR. CYRIL CLARK ▪ *ICON*

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"It's probably an error to think of drug development as a sequential activity," Dr. Clarke continues. "We may have to operationally manage development sequentially, but we should be engaged in a scientific endeavor in which all data are constantly reviewed and re-evaluated as development progresses."

Recruiting subjects and patients for early trials is one challenge, and depending upon the location, sites can be in direct competition with each other for enrollment, says Christina Fleming, Ph.D., executive VP of scientific and medical affairs, at Advanced Clinical.

"The inclusion/exclusion criteria play a big part when looking for subjects," she says. "If the demographics of the population where the site recruits are not be what the protocol requires, the site will have to broaden its recruitment area. This makes the study more expensive for the site and may lengthen the study time."

Additionally, many subjects participate in clinical trials solely as a career, making them "professional subjects" who move around the country year-round to different sites, some-

times following the seasons, looking for new trials.

"Since there is not a database that links the Phase I units collectively, this can present a challenge when trying to determine the last date a subject was in a prior study," Dr. Fleming says. "The type of study, location, unit, length of time, inpatient or outpatient, number and type of assessments, and stipends are all factors that the subjects may consider when deciding on participation in a study."

Dr. Geoffroy says constructing appropriate databases is essential to timely recruitment, particularly for specialty populations, such as recreational drug users or specific ethnic populations.

"In addition, establishing networks with local healthcare providers and hospitals allows Phase I sites to recruit patient populations for bridging studies," he says.

Best Practices for Improving Efficiency

Jeff Miller, M.D., chief medical officer at Chorus, Eli Lilly and Co., says additional goals should be added to the Phase I goals of assessing safety, pharmacokinetic (PK) parameters, drug metabolism, food effect, and drug-interaction potential in healthy subjects.

"Most importantly, drug-target engagement should be demonstrated using biomarkers of acute pharmacological response," he says. "The drug exposure needed to optimize this response should be described by pharmacokinetic/pharmacodynamic (PK/PD) modeling. The variability of pharmacological response should be characterized in light of the apparent window between target engagement and safety limits. In some cases, a patient population with disease-related pathophysiology or longer durations of dosing may be necessary, and these should be included in the Phase I program."

Dr. Miller says sponsors should assess, before Phase II, whether adequate target engagement may be achieved with an acceptable therapeutic index, a practical dose regimen, and a manageable degree of PK/PD variability.

"This has been referred to as demonstration of proof of mechanism (POM)," he says. "While rigorous statistical powering is difficult in small Phase I clinical studies, sponsors should enforce attrition for drug candidates that do not present an acceptable profile in this regard. To avoid increases in the cost and cycle time due to more ambitious Phase I development, sponsors should assess target engagement and therapeutic index first, while deferring other biopharmaceutical activities — food effect, drug interaction, formulation development, drug metabolism — until after POM. Projects with favorable POM may warrant additional studies to enhance the Phase II package, whereas unconvincing POM data may warrant limited investment and a lean proof-of-concept trial."

Dr. Geoffroy says one best practice is to add bridging cohorts/arms to early safety studies to assess drug-specific issues such as special pharmacokinetics/populations, pharmacogenomics, or proof-of-mechanism/efficacy.

"These data can guide later development decisions, such as targeted indications and the need for special safety studies, as well as save time and starting costs of performing separate studies," Dr. Geoffroy says. "In addition, careful design and implementation of the protocol will avoid extra time spent later in the clinical study. Many pharmaceutical sponsors, particularly smaller companies, may have limited experience in designing and conducting Phase I studies. Allowing CROs to use their best practices and efficiencies in conducting these studies, which have been developed from years of Phase I experience, will result in smoother and more rapid study completion." PV

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