BY DENISE MYSHKO

PHASE I: From Animals to First-in-Human Studies

More rigorous and more complex Phase I trials can be more costly and time-extensive, but they can also provide an opportunity to see proof of concept sooner.

The simple study designs of the past have been replaced with more complex designs with the addition of more screening and study procedures, biomarkers, and pharmacokinetic samples requirements, as well as longer study exposure periods.

The trend today is conducting more rigorous, early-phase clinical research that will help biopharmaceutical companies identify and select the most promising new compounds, says Michelle Middle, MB, Ch.B., corporate VP and worldwide head of early phase at Parexel International.

"The growing interest in proof-of-concept studies in targeted patient populations, which are designed to demonstrate early signals of efficacy, is helping biopharmaceutical companies to avoid costly late-stage clinical development failures," she says. "Geographic strategies and conducting multisite studies are playing a larger part in providing rapid access in the early phases to specialized patient populations. Additionally, the industry is starting to harness the power of customized solutions, such as the appropriate use of biomarkers and adaptive trial designs, to produce more robust study information in early-phase development."

FAST FACT

THE SHARE OF NEW SELF-ORIGINATED DRUGS THAT WERE TERMINATED DURING PHASE I AND PHASE II CLINICAL TESTING INCREASED FROM 1993-1998 TO 1999-2004.

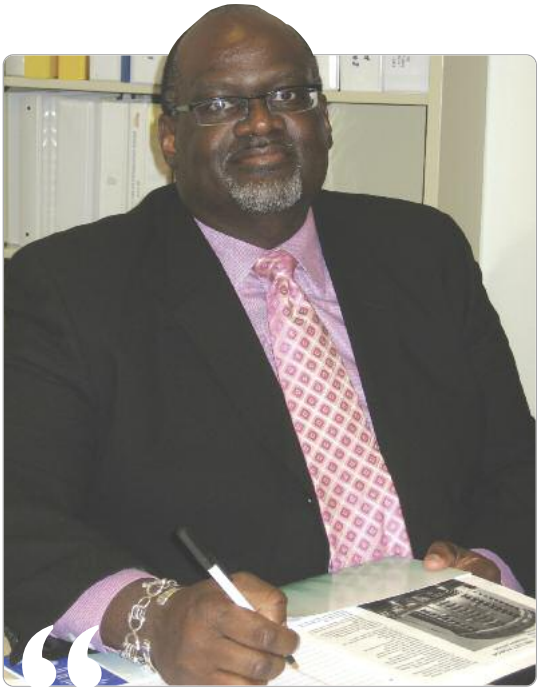
Source: Tufts CSDD

In proof-of-concept trials, a drug is given to humans for the first time in a small group of patients or healthy volunteers to verify the mechanism of action and to get an early readout of the efficacy of the compound in human disease.

There are an increasing number of studies that have both a Phase I component and a proof-of-concept component, or Phase IIa, says Jerome Bailey, VP, early phase business center, Omnicare Clinical Research.

"Anecdotal data show there has been an increase in the number of Phase IIa studies once the Phase I study has been completed and before a large Phase IIb is undertaken; this can save sponsors and CROs the cost associated with delaying or stopping a project because of safety concerns," he says. "Sponsors are more willing to spend funds on smaller proof-of-concept studies that provide an even higher level of assurance that the product is safe and shows efficacy."

There is more science now involved in Phase I than ever before, says Brian Sanderson, M.D., medical director, Chiltern Early Phase.



JEROME BAILEY
Omnicare Clinical Research

"There are an increasing number of studies that have both a Phase I component and a proof-of-concept component, or Phase IIa."

"For example, new technologies, such as PET scanning and functional MRI scanning, have resulted in the ability to assess the effects of CNS-active drugs on the ability to penetrate the appropriate functional areas of the brain," Dr. Sanderson says. "While this technology comes at a cost, it adds value in confirming proof of concept at a far earlier stage in development. In the future, the biggest challenge might be keeping up with the pace of change and what may become the explosion in biomarker technology."

Phase I: Regulatory Issues

In 2006, the FDA issued its guidance on

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Kendle

One of the significant challenges in Phase I is the need to include more and more early indicators of safety, proof-of-concept, and efficacy."

EDDIE CAFFREY
Quintiles

Investment in intelligent, early-stage development is vital to the success of any drug development program."

exploratory IND studies with the goal of making the approach to early-stage and pilot clinical trials more flexible within the context of current regulations. An exploratory IND is conducted early in Phase I, involves very limited human exposure, and has no therapeutic or diagnostic intent.

Exploratory IND studies can help identify, early in the process, promising candidates for continued development and eliminate those lacking promise. As a result, exploratory IND studies may help reduce the number of human subjects and resources, including the amount of candidate product, needed to identify promising drugs.

"These studies may be important vehicles for proof-of-principle pharmacodynamic investigations of highly potent molecules, for bioavailability studies that require only a single drug dose to be administered, and for imaging trials that permit critical dosimetry and biodistribution investigations of new molecules," says Peter Smith, Ph.D., senior VP, nonclinical development sciences at Millennium Pharmaceuticals: The Takeda Oncology Company.

He emphasized that the pharmaceutical industry could be taking greater advantage of exploratory studies to help overcome some of the time and cost challenges of drug development — in other words, to make go/no go decisions faster.

Dr. Smith says these preliminary clinical studies would allow drug developers to more quickly screen potential drug candidates and pinpoint those with the greatest promise, or identify those that show little potential and should be stopped.

This is useful for companies without confirmed high-level predictive capabilities on the nonclinical side.

There is a growing recognition that using the principles of the exploratory IND to ask fundamental pharmacologic questions about a new target earlier than has been typically done in the past can be a highly advantageous way to approach drug development, says Jamie Dananberg, M.D., executive director of clinical pharmacology at Eli Lilly and Company.

"There continues to be an ongoing dialogue around the use of exploratory and Phase 0 studies to help address critical questions in drug development," Dr. Dananberg says. "The industry as a whole has been moving to conduct studies as early as possible in development in the hopes of improving the chances of advancing successful candidates further."

Dr. Dananberg says Lilly has used the exploratory IND a number of times, principally in the areas of radiology and PET tracers used in many of the company's neuroscience programs.

"Other companies are using the exploratory IND to study varying formulations of the same new chemical entity and to explore simple pharmacologic properties of second-generation molecules to understand their potential advantages or disadvantages," he says. "Although the exploratory IND does streamline the path to explore drug development questions clinically and the investment necessary are large enough, the limitations are great enough, that the niche of opportunities is relatively small."

Phase I: Challenges

The main challenges currently in Phase I surround how to maximize the information gained to add value to the drug-development process, Dr. Sanderson says.

"This comes down to smart study design," he says. "Phase I studies should be viewed beyond being a regulatory necessity and as a key point in drug development. It is the first time the candidate drug is given to the species for which it is intended: man. During the first-in-man or Phase I stage, the new chemical entity formulation is usually crude — often a simple oral solution, made with bulk drug. Considering that up to 40% of NCEs fail in Phase I because of inappropriate pharmacokinetics, companies do not want to invest large sums of money in a drug that may still fail. The counterargument is that the crude formulation may be the reason for the inappropriate pharmacokinetic profile, while a refined for-

COMPANIES TERMINATING UNPROMISING CANDIDATES

Large pharmaceutical firms, under pressure to bring new medicines to market faster, have been getting more drug candidates to development in recent years and have become more aggressive in terminating unpromising candidates, according to a recent study by the Tufts Center for the Study of Drug Development.

One in six self-originated compounds that entered clinical testing at large pharmaceutical companies from 1993 to 2004 was expected to eventually attain marketing approval.

The study found that the in-licensing of products into the clinical pipelines of the top 50 firms, a practice that gained much industry attention in recent years, reached a high point at the end of the 1990s. After peaking at 28% for drugs that first entered clinical testing in the 1999-2001 period, licensed products as a share of the total development portfolios of big pharma dropped to just under 16% for 2005-2007.

Other findings:

- For the top 50 global firms, the annual rate at which drugs enter clinical testing increased 31% from 1999-2001 to 2002-2007.
- Nearly three-quarters of the drugs in the portfolios of the top pharmaceutical firms that reached clinical testing from 1993-2007 originated in and were developed by the firms.
- While clinical success rates for drugs varied widely by therapeutic class, of six specific broad therapeutic categories analyzed, oncologic/immunologic and central nervous system (CNS) had the greatest number of drug candidates entering clinical testing over the 1993-2007 period.

Source: Tufts Center for the Study of Drug Development. For more information, visit csdd.tufts.edu.

DR. JAMIE DANANBERG
Lilly

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mulation might demonstrate a more appropriate profile, thereby ensuring that the formulation and route of administration are appropriate with a quality formulation, which will maximize the return from even a traditional Phase I safety and PK study."

Companies large and small want to know that their drugs are safe and show efficacy in the target therapeutic area as soon as possible.

"This can be achieved by understanding what the biological target for the disease in question is and assessing this in a non-therapeutic Phase Ia/Ib trial either in healthy volunteers or in healthy patients who have the disease in question," Dr. Sanderson says. "This means academia and commercial research need to work in collaboration to identify biological targets, validate them, produce suitable biomarkers for the target to assess/measure any pharmacological effect on them, and develop compounds for these targets."

Kerri Schoedel, Ph.D., scientific director, clinical pharmacology, at Kendle, says one of the significant challenges in Phase I is the need to include more and more early indicators of safety, proof-of-concept, and efficacy.

"These assessments are highly relevant for later decision-making, but good planning capabilities and scientific/medical expertise are needed so that participant safety and study practicality are not sacrificed," she says.

Dr. Dananberg says another major challenge in Phase I development applies specifically to therapeutic antibodies or biologics with long half-lives.

"In order to meet the primary safety objectives during this phase of development, it is necessary to observe these compounds for much longer periods and escalate dosing more conservatively," he says. "This adds significant time to the development timelines of these entities."

Over the last few years, further trial objectives have been added to Phase I studies to not only characterize the pharmacokinetics of the drug but also determine some measure of effect through the monitoring and modeling of biomarkers, says Murray Ducharme, Pharm.D., chief science officer for Cetero Research.

"One novel solution is the use of a hybrid study," he says. "Hybrid studies essentially combine the first-in-human, pivotal PK, and proof-of-concept studies into a single trial. With the right design and access to patients, researchers get valuable insights into their drug candidate within six to nine months, shaving three to six months off the normal development timeline."

Alan Copa, Pharm.D., president of clinical operations for Cetero Research, says another challenge is having participant and patient databases up to date to ensure that the pool of subjects is large enough and broad enough for a variety of study populations.

"It's important to make sure that enough participants are being screened to ensure that the study can start full and on time," he says. "If enough participants aren't screened for inclusion in a study, the study will be delayed. Another challenge that is often overlooked is the personal side of clinical research. Fostering a positive relationship with participants encourages a safe and welcoming experience for them."

Phase I: Best Practices

Investment in intelligent, early-stage development is vital to the success of any drug development program because it sets the stage for more productive and successful Phase II/III trials, says Eddie Caffrey, global head of Phase I at Quintiles.

"Given that there are numerous objectives in Phase I, it makes sense to take an integrated approach," he says. "Specialist techniques in translational medicine such as PET, pharmacokinetic and pharmacodynamic modeling, the use of biomarkers, and the inclusion of patient groups, often in integrated protocols, help to provide proof of concept early."

Dr. Sanderson says there has been an emergence of multifunctional, or "umbrella," protocols particularly in Phase I.

"These involve the combination, in a single study, of the traditional ascending dose study with the first-in-man multiple-dose tolerance study," he says. "The use of these crossover designs coincides with the drive by the industry to achieve more with such studies. This newer thinking in the study design and the use of crossover studies is one way that Phase I studies can become more efficient. The advantages are that such studies require only one regulatory approval and ethical review, there is consistency in the inclusion/exclusion criteria, and they are quicker to perform. In addition, all parts of the study can be managed by the same project manager and team and be conducted by the same center and the same investigator, all of which promote operational efficiencies and save time."

Dr. Dananberg says there are several areas where careful planning and implementation can continue to improve Phase I development in both scientific and operational aspects.

"First, as we continue to expand the use of Phase I research to explore pharmacodynamic signals, it is essential that the biomarkers, methods, and technologies used to detect those signals are fully qualified before the start of the initial drug candidate clinical trials," he says. "Second, improving the coordination of data collection and analysis is important, as it applies to dose-escalation, cohort recruitment, and even in the move from single- to multiple-dosing studies. Integrating the single- and multiple-ascending dose elements of Phase I research is a particularly useful tool to improve overall efficiency as well. Third, building a well-defined set of clinical research units with specific sets of capabilities and unique expertise is a key mechanism to running this phase efficiently. Finally, running the business with optimized processes that support the unique aspects of Phase I research is a critical aspect of improving productivity."

The key to improving the efficiency of Phase I clinical development is to establish a strong relationship with a Phase I unit CRO that can also manage later-phase studies, says Nancy Boman, M.D., Ph.D., VP, clinical development and regulatory affairs, at Acucela.

"It's essential to have a clear clinical development plan in place before embarking on the Phase I study," she says. "Where possible, it's important to use standards — including case report forms, exported datasets, monitoring guidelines, etc. — so that minimal reworking is required for future studies. I also recommend making sure that the oversight team encompasses a broad area of expertise, including clinical pharmacology, clinical operations, and other standard clinical research functions." ✦

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