Slow Start to Phase 0 as Researchers Debate Value

Investigators can now add another phase to their clinical trials testing. The question is how many cancer researchers will take that option?

The new choice is the so-called phase 0 trial, which allows researchers to test a small drug dose to see if it behaves as expected in humans without going through the more stringent requirements of a phase I trial. Proponents say it will quickly weed out drugs that are metabolically or biologically ineffective and give drug companies faster insight into whether to move forward with trials. Opponents, mostly cancer researchers, say it won’t save money or time because scientists don’t yet understand enough about how most how targeted therapies work to know whether they can even learn from low-dose tests.

Such phase 0 trials highlight a big problem in oncology drug development and may put researchers in a bind, said Richard Schilsky, M.D., a professor of medicine at the University of Chicago Hospitals and chairman of the Cancer and Leukemia Group B clinical trials group. “We are clearly in need of further advances because there is still an insufficient understanding of tumorigenesis, yet there are also a lot of people waiting for the FDA to do something to make the drug delivery system faster and more efficient.

“Phase 0 is clearly not the major retooling of the drug development process that we have been waiting for and which will help us,” Schilsky said.

The Food and Drug Administration issued the new industry guidelines for early exploratory drug studies in mid-January, a move it says will help pump up the volume in the nation’s drug pipeline, which has slowed to a trickle. Last year, only 20 new drugs were approved, compared with 36 in 2004 and 53 in 1996.

The new program is one of the first changes promised by the agency in 2004, when it embarked on its Critical Path Initiative to modernize the clinical trials process. The guidelines established the “exploratory” investigational new drug (IND) study—since dubbed a “phase 0” clinical trial—that the FDA hopes will allow researchers to quickly establish whether an agent of interest works as desired within humans and thus could potentially offer a clinical benefit.

The phase 0 strategy requires fewer preclinical animal studies than a typical phase I trial and allows researchers to make smaller batches of an experimental drug under relaxed guidelines. To offset safety concerns, the human tests would be limited to a few volunteers, a short time frame (no more than 7 days), and a reduced dose that ensures no adverse toxic effects. One option the FDA is encouraging—and has been available to European researchers for several years—is “microdoses,” less than 1% of what researchers expect would be the agent’s standard dose.

The FDA’s David Jacobson-Kram, Ph.D., said a phase 0 trial would allow researchers to judge quickly whether an agent has the right pharmacokinetics (the body’s effect on the drug) and pharmacodynamics (the drug’s impact on the body) to make it a contender. For example, a phase 0 clinical trial could tell researchers if a drug is entering the bloodstream as it should or if it interacts with a key enzyme. But it would not tell investigators the drug’s impact on the target disease, and it would not replace the traditional dose escalation, safety, and tolerance studies now required in phase I testing.

Even if it doesn’t eliminate steps, an exploratory IND study could help to reduce the cost, time, and inefficiency of current drug development because it could eliminate candidate drugs before they ever reach phase I testing, said Jacobson-Kram, associate director of pharmacology and toxicology in the FDA’s Office of New Drugs. Most agents fail in clinical testing because they do not behave as predicted in animal studies. Exploratory IND studies can help investigators choose among more or less effective compounds before drugs are made to an exacting standard and before all the required small and large animal preclinical work is undertaken, he said.

“Current drug testing is turning out to be very inefficient and very expensive. Way too many drugs are failing late in development, which is costly for all of us,” he said.

The National Cancer Institute, which worked with the FDA on the guidelines, is embracing exploratory IND studies, said Joseph Tomaszewski, Ph.D., chief of NCI’s Toxicology and Pharmacology Branch.

“We look at it as a way to get human information faster in the development process.”

The Pharmaceutical Research and Manufacturers of America (PhRMA) has also offered its blessing. Preparation for a typical IND study involves a great deal of expense before there is any idea of how the drug will perform in humans, said Caroline Loew, Ph.D., PhRMA’s senior vice president for scientific and regulatory affairs, whereas the exploratory IND study
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offers companies a crystal ball that can save them time and money.

“We think this is a great step forward.”

Enthusiasm Varies

Even though researchers have been able to use phase 0 testing for more than a year—the FDA said in early 2005 that its rules permitted such tests, and the guidelines formalized that opportunity—Jacobson-Kram acknowledges there has been a slow reaction.

“The response we have gotten from commercial sponsors and from investigators has not been at the level we expected,” he said. Although the FDA does not yet have a system in place to track applications for exploratory IND studies, Jacobson-Kram thinks few have been submitted.

Loew said that PhRMA members know about exploratory IND studies—and that a few are in the works—but that it will take time for industry to adapt to them. Opinion varies as to how valuable they will be for specific development programs, Loew said, but added that “over time, it will be used more and more.”

The FDA, NCI, and PhRMA representatives acknowledge the arguments against using phase 0 testing. One is that a low dose may not tell you the information you need to judge efficacy. And exploratory IND studies are extra work—even if successful, they do not shorten the requirements that are still needed for a full IND application: finishing preclinical studies, preparing the agent to manufacturing standards, and so on.

Several academic oncology researchers cited these concerns and others when they questioned if a phase 0 study could be useful in testing cancer drugs. Healthy volunteers could not be used, which means recruiting cancer patients for the study and reducing the pool potentially available for phase I–III testing, some researchers argue. Others add that sick patients may not jump at the chance to take a low dose of an agent that likely would not help them.

Their biggest concern is that a small dose of a novel cancer drug could not provide meaningful information given that most current agents do not have validated biomarkers that predict tumor activity with sufficient accuracy.

“The assumption is that you have some measurement, either biological, pharmacological, or imaging, that helps you determine whether a drug is hitting a target and having its desired effect,” said Mace Rothenberg, M.D., professor of cancer research at Vanderbilt-Ingram Cancer Center. “But in oncology, we just don’t have that for many of our targets now. This is not like testing an antidepressant and seeing whether it increases serotonin transmission.”

Because reliable and validated assays are not currently available even for most approved targeted cancer drugs, Rothenberg suspects that many experimental drugs will fail phase 0 testing.

“Instead of studies becoming more efficient, there is just as great a chance that we could misidentify active drugs as inactive,” he said.

Responding to Critics

In fact, the point of phase 0 testing is that that investigators need to know their targets before testing, argues the NCI’s Tomaszewski.

“This is a way to start changing the way we look at the lot of these agents. This approach may not get you faster into the clinic, but it will get you there more rationally,” he said. “The real
problem today is that most of the research that is done suffers from a lack of rigor. Investigators don’t know what to look for in an agent.”

Jacobson-Kram puts the issue a different way: “If you are shooting darts but don’t know where the board is, then what is the point of the game?”

The University of Chicago’s Schilsky acknowledges that investigators need more information about how new drugs work, but requiring them to know that up front may at this point be punitive.

“This will save some money for some sponsors, but in most circumstances, it will not be that helpful,” he said.

Tomaszewski agrees with critics who say that microdosing may not be applicable to cancer research. “Microdosing may be the safest route, but the NCI is not going to do it,” he said. “We want to look at the pharmacokinetics of the agent and whether it is having an impact on the tumor, and that would not occur 99 out of 100 times with a microdose.”

The NCI will be launching its first exploratory IND study in several months and will use a dose larger than a microdose that preclinical work has demonstrated is not toxic in animals. “For a lot of targeted agents, there is a much wider gap between what is biologically effective and what produces toxicity,” he said.

If NCI’s experiment with phase 0 testing works, it may consider requiring exploratory IND studies for all clinical trials it sponsors, Tomaszewski said.

“Having agents fail early in development rather than in phase III studies could save a lot of resources, including patient resources,” he said.

—Renee Twombly