BY DENISE MYSHKO

Proof of CONCEPT

UPTAKE OF EXPLORATORY INDS, a mechanism for early development that can help determine proof of concept for a potential product, **HAS BEEN SLOW**. To capitalize on the benefits of this process, **the industry will need to change the development paradigm**.

WHAT IF PORTFOLIO MANAGERS COULD GET A SNEAK PEAK INTO A POTENTIAL PRODUCT'S PHARMACOKINETIC AND BIOAVAILABILITY PROFILE BEFORE INVESTING IN TRADITIONAL PHASE I SAFETY STUDIES?

That's exactly what some pharmaceutical companies and contract research organizations are doing. They are using a strategy called exploratory INDs to help determine whether a mechanism of action can be observed in humans and provide information on pharmacokinetics. These studies are done prior to traditional dose escalation, safety, and tolerance studies and involve limited human exposure to a product.

Exploratory IND — sometimes called Phase 0 — studies are intended to provide clinical information about a new drug candidate at a much earlier phase of drug development. Experts say the greatest value of the exploratory IND is determining proof of concept and confirming the preclinical models. In this way, an exploratory IND can be a cost-effective method to improve early assessment and weed out promising from not-so-promising product candidates.

"The fact is we're improving the quality of the data that are being generated preclinically in vitro, in cells, and then in animal models, but we realize that the data models will never fully mimic a patient," says Peter Lassota, divisional VP, imaging and oncology, at Caliper Life Sciences. "Although we are continuously improving our knowledge around why diseases happen, we're still not 100% sure that the concept is correct until we go to the clinic; at this point we can inhibit the target in man and we can correlate the phenotype with the inhibition of that target."

George Mills, M.D., VP, medical imaging consulting, for Perceptive Informatics at Parexel International, agrees that an exploratory IND is an avenue to evaluate the preclinical assessments for investigational drugs and biologics in human subjects. These confirmatory findings from an exploratory IND in the human subject enable the separation of the promising drugs from the not-so-promising drugs.

"The exploratory IND is a significant, cost-effective tool to identify the product or products that a company is going to move forward," Dr. Mills says. "A highly effective route to improve the cost-effectiveness for drug and biological development is to take away the not-so-promising products early."

While the exploratory IND has the potential to provide efficiencies over the long term, at present just a handful of companies are conducting exploratory IND studies, according to officials from the Food and Drug Administration.

"Pharma companies are accustomed to a very different development paradigm," says David Jacobson-Kram, Ph.D., associate director for pharmacology and toxicology, Office of New Drugs, Center for Drug Evaluation and Research, at the FDA. "It's hard to change a process that has been successful for a very long time. It is also hard to convert people to think positively about a process that forces products to fail early, which would allow them to move on to more promising candidates."

DR. DAVID JACOBSON-KRAM
FOOD AND DRUG ADMINISTRATION

Pharma companies are accustomed to a very different development paradigm. IT'S HARD TO CHANGE A PROCESS THAT HAS BEEN SUCCESSFUL FOR A VERY LONG TIME.

BENEFITS OF EXPLORATORY INDS

In a guidance released in January 2006, the FDA laid out specific approaches for researchers

when conducting very early clinical studies in people. The guidance, part of the FDA's Critical Path Initiative to modernize the drug-development process, contains recommendations about safety testing, manufacturing, and clinical approaches that can be used in these very early studies. This guidance allows researchers to develop a better understanding of parameters such as drug distribution, pharmacokinetics, and target localization of new agents before undertaking large-scale trials.

Thomas Lang, Ph.D., chief drug development officer at Samaritan Pharmaceuticals, says the FDA guideline is a good start, but the agency needs to broaden the parameters.

"The current guidance is too restrictive," he says. "The FDA could do more to lessen the burden to move to Phase I. The agency could make a separate category just for Phase I studies, which I believe would be useful for a lot more companies."

Exploratory IND studies have been underused by both small, medium, and large pharma and biotech companies, says Greg Gorman, Ph.D., director of the toxicology and bioanalytical sciences department at Southern Research Institute.

Experts say exploratory IND studies may help reduce the number of human subjects and resources, including the amount of candidate product, needed to identify promising drugs.

"The biggest potential benefit, in my mind, is the early proof of concept," Caliper Life Science's Mr. Lassota says. "Companies can evaluate whether there is an association between inhibition of targets and the disease. At the same time, a second benefit is the ability to select the best compound from a group of drug candidates."

Dr. Gorman agrees that the use of exploratory INDs is a good way to probe central drug candidates.

"If good results are realized from the microdosing early Phase I studies, this provides another level of confidence to move a compound forward in the drug-development process," Dr. Gorman says. "If unfavorable results are obtained, the company can take the compounds back into lead optimization and change the chemistry or decide that it makes sense not to invest any further resources in those compounds lacking promise."

Chris Elicone, senior marketing manager at Applied Biosystems, says companies might consider doing an exploratory IND if, at the end of drug discovery, they don't have any predictive preclinical animal models that will give a determinant result.

"Often, many of the animal model studies are unreliable," he says. "This unpredictability has many companies looking at the exploratory IND approach before incurring the expense of a full IND."

Dr. Mills says data from exploratory INDs can help smaller companies address investigational product performance and the financial concerns of the investment community.

"A developer would be able to demonstrate that the proposed product targets appropriately, clears from the body appropriately, and has an expected profile for safety development," he says. "This gives a very rapid assessment profile for providing investment credibility for future product development."

PHASE

Exploratory IND studies — sometimes called Phase 0 — are intended to provide clinical information about a new drug candidate at a much earlier phase in drug development.

DR. GEORGE MILLS
PERCEPTIVE INFORMATICS

EXPLORATORY INDs ARE NOT A SUBSTITUTE FOR PRECLINICAL DEVELOPMENT. They are expeditious proof-of-concept Phase I IND clinical studies that confirm preclinical findings through assessment in human subjects.

LIMITATIONS AND CHALLENGES

Experts say the use of an exploratory IND is not appropriate for every compound. Dr. Lang points out that for some companies and some products there are risks.

"Companies are taking a chance if the product is dose-response sensitive," he says. "There is a risk of using a dose that is not the right dose, for example if the dose is too low and consequently doesn't elicit the desired result."

On the other hand, Dr. Lang says an exploratory IND could be beneficial for development products in certain drug classes.

"For example, it would be great to evaluate cancer drugs based on proteins, enzymes, and other factors that have an obvious physiological effect," he adds.

The FDA's Dr. Jacobson-Kram points out that just a handful of companies are doing exploratory INDs.

"Companies that are conducting exploratory INDs don't always use them for their intended purpose," he says. "For example, if a drug is very difficult to synthesize, before investing a lot of money in making large quantities of the drug, companies want to see whether it makes sense to go forward. That's one reason to conduct an exploratory IND, but that's not one we originally had in mind when we developed the

CHRIS ELICONE
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AN EXPLORATORY IND CAN FRONT LOAD A COMPANY'S CHANCE OF SUCCESS. If the exploratory IND was configured properly to provide key results, researchers can make informed decisions and determinations leading to a greater chance of success in a full IND.

DR. THOMAS LANG
SAMARITAN PHARMACEUTICALS

EXPLORATORY INDS ALLOW COMPANIES TO CONFIRM WHAT THEY SEE IN ANIMAL MODELS. But they can run the risk of getting a negative result, which for some companies means the drug never gets developed.

PETER LASSOTA, CALIPER LIFE SCIENCES

IN AN EXPLORATORY IND, A NONTOXIC DOSE HAS TO BE USED, which means there is a possibility that there won't be any therapeutic effects and a proof of concept may not necessarily be achieved.

guidelines. The thinking at the time was to provide a mechanism that would allow companies to choose a product to take into the clinic that is the most promising based on human data. This tool is designed primarily to weed out compounds that are going to fail and to weed them out early."

Dr. Mills says companies may have an overexpectation of the data that can be extracted from exploratory INDs.

"I've heard some express concerns about the limitations of doing exploratory INDs in terms of therapeutic trial assessment," he says. "Frankly, therapeutic trial assessment is what classic Phase I and Phase II development is all about. An exploratory IND study is an avenue to evaluate the preclinical assessments of an investigational drug and to begin development in human subjects to confirm performance in the human subjects in a cost-effective manner."

Dr. Jacobson-Kram says the use of exploratory INDs may not make development happen that much faster, but they could improve development efficiencies and reduce costs by reducing the amount of resources being wasted on drugs that don't make it to market.✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

Experts on this topic

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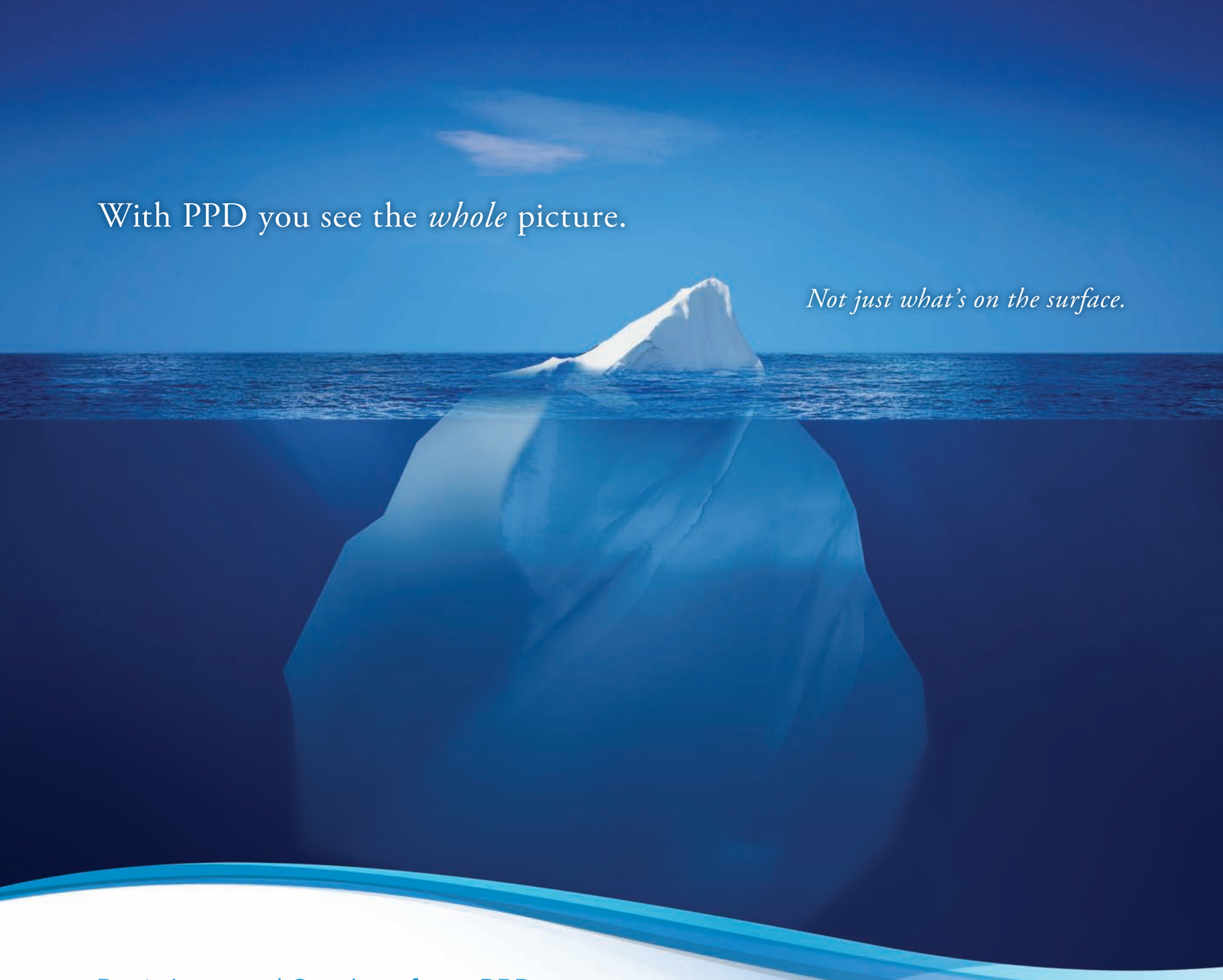

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