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In Drug Research, the Guinea Pigs of Choice Are, Well, Human

By ANDREW POLLACK

Researchers at the University of Munich repeated the experiment 70 times: a healthy volunteer would receive a chemical injection, then be left alone to ride out an artificially induced panic attack.

From the next room, doctors watched the volunteer's restlessness via video camera, measured the quickening pulse and rise in blood pressure, and used an intercom to question the person about his or her feelings of impending doom. The attacks typically lasted 5 to 10 minutes.

Each volunteer was put through the same test a few days later, but this time most of them first received an experimental anti-anxiety drug. The drug quelled anxiety well enough in those experiments last year that its developer, the Swiss pharmaceutical company Novartis, gained the confidence to conduct large clinical trials.

The company's approach is part of a trend in the pharmaceutical industry. Drug researchers are conducting small, fast, relatively inexpensive tests on people to get a quick gauge of a drug's promise before committing to full-scale clinical trials that may involve hundreds of patients, millions of dollars and many years of study. Often called experimental medicine, the approach is meant to reduce the huge costs of drug development and speed the most promising treatments into the marketplace.

In the past, many of the tests might have been done only on animals. That might seem to raise ethical concerns, but the people who regulate and monitor drug experiments say that no problems have risen so far. And scientists and industry executives, while acknowledging the potential for ethical issues, say that experiments on people are more reliable, because animal tests often fail to accurately predict whether a drug will work on people.

"Humans are the experimental animals here," said Roger Perlmutter, executive vice president for research and development at Amgen, a large biotechnology company that has embraced the new approach.

Amgen, for instance, gave different potential arthritis drugs to human volunteers and then used a blood test to gauge the best one to take forward into clinical trials. The results were almost the opposite of what Amgen found when it conducted similar tests in animals.

Pfizer has done experiments in which volunteers who took drugs were injected with radioactive tracers and given PET scans to see if the drugs were reaching their expected targets in the body. The company has abandoned several drugs that did not, said Stephen A. Williams, who directs clinical technology for the company.

It is too soon to know whether experimental medicine will really transform drug development. But the industry needs to do something. Despite rising research and development spending, last year only 21 new compounds were approved as drugs, compared with more than 30 a year in the late 1990's.

All clinical trials, of course, are experiments on people. But subjects might be exposed to more scans, blood tests and biopsies than in a more conventional trial.

"The treatment burden on the patients goes up," conceded Stephen Dilly, who runs drug development at Chiron, a biotechnology company. "You're squeezing the last drop of data out of every patient you treat."

But because the experiments are carefully monitored, many experts say the patients face no higher dangers than with medical research generally. "These kinds of studies don't really have that much higher risk than the other studies,'' said P. Pearl O'Rourke, director of human research affairs for Partners Healthcare, which runs some of the Harvard teaching hospitals.

Like others in the field, Dr. O'Rourke, who helps review and monitor human research conducted in hospitals including Massachusetts General and Brigham and Women's, says the early tests might mean fewer people over all are exposed to experimental drugs, by weeding out dead-end drugs before larger trials begin. "We may be asking a small number of individuals to participate in a more meticulous study that perhaps in the past took us 2,000 patients to answer,'' she said.

In these new, highly exploratory studies, the subjects may sometimes be perfectly healthy volunteers - as in the anxiety-drug experiment. In other cases, as with cancer therapies, the participants are usually people already afflicted with the illness being studied.

As with full-scale trials, the clinical experiments, which can be part of conventional trials or done separately, must be approved by the Food and Drug Administration and by review boards at each trial site.

Pat El-Hinnawy, a spokeswoman for the federal Office for Human Research Protections, said officials there were not aware of any problems arising from such experiments.

Lawrence J. Lesko, director of the office of clinical pharmacology and biopharmaceutics at the F.D.A., said the procedures used "don't seem to be overly burdensome and invasive." He said some patients have concerns about their genetic data being shared with others but that companies take steps to protect such privacy.

One volunteer, Ken Garabadian, who has an intestinal tumor, said he was glad to participate in a study of an experimental cancer drug from Bristol-Myers Squibb, even though it will mean a biopsy, a gene test and at least a couple of PET scans.

"There's always a risk, but there's a larger risk when you don't do it," said Mr. Garabadian, 54, a gasket salesman from Bellingham, Mass. "I don't feel like you go into these things feeling like a guinea pig."

Only about 8 percent of drugs entering clinical trials now make it to market, according to the F.D.A., and companies want to be able to spot losers before a lot is spent.

"What is the biggest single cost in drug development?" said Jeffrey M. Leiden, president of the pharmaceutical group at Abbott Laboratories. "It's late failures."

Even a small improvement in the ability to predict failures could save $100 million in development costs per drug, the F.D.A. said in a March report. In an expansion beyond its usual role of regulating drugs, the agency said it planned to help the pharmaceutical industry develop techniques to speed drugs to market, including ways to predict safety and effectiveness early.

The move toward human experiments is also being driven by new technology that makes it possible to better assess the effect a drug is having inside the body. So-called gene chips, slivers

of glass containing strands of DNA, can measure which genes are turned on or off in the body after a drug is taken.

And new forms of imaging go beyond merely visualizing anatomical structures, as X-rays do, to showing processes inside the body, sometimes at the molecular level. Functional MRI, a variation on the common form of medical imaging, can show which areas of the brain are spurred into action by a drug. Positron emission tomography, or PET, can be used to tell if a drug is binding to the target protein in the body.

Pfizer is now building a research center in New Haven to perform early stage drug testing, with PET scanning provided at nearby Yale University. GlaxoSmithKline is building a clinical imaging center with Imperial College London.

Another imaging technique, called optical coherence tomography, is being used to study the effect inside the eye of a drug that Genentech is testing to treat macular degeneration, a retina-damaging disease that can cause blindness. Anatomical changes can be seen with the tomography in a week or two after the drug is given, while an effect on eyesight might not be evident for a couple of months, according to Philip J. Rosenfeld, a trial investigator at the University of Miami.

In the future, genetic tests, images or other "biomarkers" of a drug's effectiveness might be used by the F.D.A. to approve drugs, which could mean a huge acceleration in drug development. Already, for instance, AIDS drugs can be approved if they reduce the level of the virus and raise the level of immune system cells in the blood, without having to wait years to see if the drugs prolong survival.

But before that could happen the F.D.A. would need more proof that the markers correlate with a meaningful benefit to patients, Dr. Lesko said. To win approval of its drug, for instance, Genentech will have to show it improves vision, not just that it causes anatomical changes in the eye.

At the Dana-Farber Cancer Institute in Boston, where Mr. Garabadian is being voluntarily tested, scientists are using PET scans to quickly determine if drugs work against a type of cancer called gastrointestinal stromal tumor. The PET scan can detect the uptake of glucose, which tumors need to nourish their growth.

Using such scanning, Dana-Farber researchers discovered a few years ago, to their amazement, that glucose uptake had stopped - a sign the tumor was dying - as early as one day after some patients took the Novartis drug Gleevec. The more conventional way to tell if a cancer drug is working - waiting for a tumor to shrink - can take weeks, said Annick D. Van den Abbeele, the director of nuclear medicine and PET at Dana-Farber.

Since the Gleevec tests, the Dana-Farber scientists have used the technique to quickly establish effectiveness of a Pfizer drug, SU-11248. Now they are testing one from Bristol-Myers, BMS-354825, which Mr. Garabadian is receiving.

The trial is a phase 1 clinical trial, which usually tests only a drug's safety. But on top of those safety tests "we put an extra layer of biologically exciting testing," said George Demetri, director of the sarcoma center at Dana-Farber.

Mr. Garabadian also took part in the studies of the Gleevec and Pfizer studies. Both drugs worked for a time, though eventually his cancer worsened again. Mr. Garabadian said that when the PET scans gave him an early sign the drugs were working "the psychological boost was just enormous."

Experimental medicine is changing the old linear pattern of drug testing: first in animals; then phase 1 trials in people to test safety and help determine the dose; phase 2 trials to test efficacy and determine optimal doses; and finally, phase 3 trials involving large numbers of patients in

which the drug is often compared with another drug or a placebo.

While not abandoning animal studies, scientists might now move back and forth between animal and human studies. Phase 1 trials might be used to gauge efficacy, not just safety. In some cases, human testing is being done even before a drug is given - for example, to validate the imaging system that will be used in the trial. Some scientists call these "phase 0" trials.

Some companies are also using imaging to help determine the proper dose of drugs by seeing how much drug it takes to saturate the drug's target in the body. Merck found that in some cases it needed far lower doses - which usually means fewer side effects - than if using the more typical criterion of how much the patients could tolerate, said Richard Hargreaves, the company's executive director for imaging.

In some cases, experimental medicine can raise the cost of early trials. PET scans, for instance, cost about $5,000. Dr. Dilly of Chiron said a phase 1 trial with imaging and genetic tests could cost nearly $100,000 a patient, compared with $10,000 to $15,000 for a standard trial.

But executives say those expenses are trivial if they allow the company to avoid an unsuccessful multimillion-dollar clinical trial later.

The impact of experimental medicine could become clear in a few years, as the early drugs that have gone through the process move closer to market. "We are going to find out in five years," said Dr. Hargreaves of Merck, "whether we've done the right thing."