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TODAY'S FORECAST: Sunny and breezy with cool temperatures. at 7 A.M. 25° | at 2 P.M. 40° | at 7 P.M. 32° DETAILS, PAGE 37

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Drug makers now confront unlikely foe in labs: Science

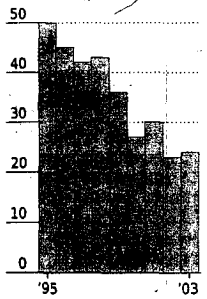
Discovery of medicines slows despite billions in investments

BY KITTA MacPHERSON AND ED SILVERMAN
STAR-LEDGER STAFF

For the past 10 years, Janet Woodcock, one of the Food and Drug Administration's top officials, has maintained "The List," a catalog of diseases that desperately need new treatments.

It's a sorry compendium of incurable illnesses. Advanced breast cancer. Alzheimer's. Autism. Adolescent depression. Diabetes. Lupus. Multiple sclerosis. Obesity. Schizophrenia.

Slowing down
New drugs submitted to the FDA for review.



THE STAR-LEDGER
SOURCE: FDA documents

Woodcock's hope is to cajole the drug industry into forging a golden age of discovery, something supposed to have happened by now.

But the reality is that the pharmaceutical industry isn't about to produce miracles anytime soon. The word inside labs, corporate board rooms and regulatory cubicles is hauntingly consistent: The science is too difficult.

"The low-hanging fruit is all gone, and the unique opportunities are difficult to come by," said Irwin Lerner, a former chief executive at Hoffmann-La Roche, a Swiss drug maker with U.S. headquarters in Nutley. "There's been a real failure that, despite billions of dollars in investment, research hasn't conquered the diseases that haunt us."

Or, as Woodcock, director of FDA's Center for Drug Evaluation and Research, says, "Some of these things are going to be really hard."

Like an oil pipeline running dry, the number of important new medicines generated by pharmaceutical laboratories has slowed to a trickle at a defining moment for the industry. New concerns about product safety, pricing and government oversight have thrown companies under piercing scrutiny and raised new questions about their lack of innovation.

Even scientists from leading drug firms admit

[See **MEDICINES,** Page 28]

MEDICINES

CONTINUED FROM PAGE ONE

their spark has been snuffed.

According to a survey published last week by Kline & Co., a consulting firm in Little Falls, scientists claim they are working harder and completing more projects, but they also believe research and development productivity has dropped.

"In an increasingly difficult market with exceptionally high expectations, they admit they need help," said Steve Chen, industry manager for Kline's health care division.

Finding a way to refuel the drug pipeline is imperative, experts say, because:

■ The pharmaceutical industry is the world's medicine chest. If firms stopped providing truly innovative treatments, many hoped-for medical advances would never materialize. It is not an exaggeration to say millions of lives hang in the balance.

■ The lack of new drugs hurts companies' abilities to grow, which could lead to downsizing or more consolidation among the remaining drug makers. Either would offer an ominous forecast for New Jersey, where the industry employs about 65,000 people.

■ Industry critics suggest a lack of new products can tempt pharmaceutical executives to be slow in pulling popular products from the market when safety issues arise. Pharmaceutical officials strongly deny this suggestion.

■ Without pharmaceutical innovations, health care costs will continue to rise because more patients will require hospital stays rather than be treated with medication.

Faced with this clogged pipeline and other pressures — notably investor demands for consistent profits — the big drug companies are changing the way they do business.

There has been a recent lust for mergers, where companies acquire rivals mainly for one or two big-selling products. There is an emerging pattern of companies turning their backs on new treatments deemed not profitable enough. And companies are investing heavily in biotechs, whose smaller, nimble operations yield some of the most promising treatments.

These new moves, experts like Lerner say, may not be enough to generate the new drugs demanded by patients and investors, and the stakes are enormous. Already, half of all Americans take at least one prescription drug and 50 percent of seniors rely on three or more, according to industry statistics.

ARISTIDE ECONOMOPOULOS/THE STAR-LEDGER

Neuropsychiatrist Peter Mueller conducts a session in his Princeton office. Mueller cannot persuade the maker of the drug Meridia to investigate his beliefs that the medicine can treat post-traumatic stress disorder, fibromyalgia and Tourettes.

This paucity of invention is a hot topic in the pharmaceutical industry, but mostly behind closed doors.

"It's the billion-dollar question that no one in the industry wants to talk about," said Peter Rost, a Pfizer vice president of marketing.

"How many breakthrough drugs have there been in recent years?" asked Barbara Brenner, a patient activist and executive director of Breast Cancer Action in San Francisco. By "breakthrough," she means fulfilling a genuine, unmet need, not a "copycat" drug.

"I can only think of three," she said. "Gleevec, Herceptin and the aromatase inhibitors. That isn't much, considering the public investment. All of the areas they are looking at now, including cancer, are much more complicated than the problems investigated in the past."

Gleevec is a leukemia drug made by Novartis. Herceptin, a Genentech product, treats some forms of breast cancer. Aromatase inhibitors are a new type of breast-cancer treatment made by several firms.

MILLION-DOLLAR BABY

Breakthrough drugs are difficult, risky and expensive to discover.

The Tufts University Center for the Study of Drug Development, a Boston-based think tank, estimates it costs about $800 million to bring a drug to market, where it can be sold exclusively for up to 20 years, sometimes more, until its patent expires. Combine that with the scientific difficulties that must be conquered and it's little wonder, experts say, that companies are more reluctant to take big risks.

"Working on treatments for chronic diseases has a better potential economic payoff, but companies are looking for opportunities to fulfill unmet medical needs," said Alan Goldhammer, a spokesman for the Pharmaceutical Research and Manufacturers of America in Washington, D.C., the industry trade group.

Drug companies got a taste for the easy hit more than a decade ago with medical advances into the workings of the cardiovascular system. This resulted in drug makers scrambling to develop their own medications to treat ailments, such as high blood pressure and cholesterol.

Beyond heart disease, there were new pills for allergies, chronic pain and new "lifestyle" drugs — a category that would continue to grow with importance. The era of the blockbuster drug had dawned. Think Lipitor or Zoloft or Norvasc.

Times were good. Profits were high. Investors were happy. The drug companies heavily promoted medications to doctors and consumers.

The money flowed.

To peddle these new products, pharmaceutical companies needed large sales teams and marketing budgets to consistently deliver the big profits Wall Street expected.

The excitement was not limited to the marketing folks.

Researchers stepped up their hunt for new drugs. Pulling drug candidates from their vast libraries of compounds, they used the "spray and pray" technique, lacing petri dishes laden with disease agents with slightly varying sequences of experimental compounds and watching what happened.

In 1996, companies filed 45 applications to the FDA to review "new molecular entities," one of the most ever for new drug compounds. The figures remained high — until recently. The number of

[Continued on next page]

CONTINUED FROM PAGE 28

applications bottomed out at 23 in 2002 and remains low.

Also worrisome is that new drugs are failing safety tests at a higher rate than in the past. In the 1980s, about 14 percent of all drugs submitted for review were approved. Today the success rate has dropped to about 8 percent. Approximately 50 percent of new drugs fail to produce adequate evidence of safety and effectiveness in the late stages of Phase 3 studies, and cannot be approved, according to the FDA.

Like a savvy Broadway producer with a hit and eager investors waiting in line, drug makers soon found it harder to churn out smash after smash.

Ultimately, the companies found it's "very difficult to feed that large giant," said Ray Zoeller, vice president of planning and business development for Thomson Healthcare, a publishing company that closely tracks the industry.

THE PICASSO PILL

Leads for new medicines began slowing just as pressure was building pipelines to spit out the next round of big sellers.

Look at the problem this way: If a drug maker rings up $30 billion in sales each year, the surest way to achieve at least the 10 percent growth Wall Street expected is to come up with one blockbuster. Even a drug that generates $150 million in annual sales won't move the meter very much.

For that reason, drug makers became quicker to reject safe and effective pills that had poor big-profit potential.

"Every blockbuster is a Picasso painting," said Rost. But, as the Pfizer executive cautioned, "You can't produce a Picasso on a conveyor belt."

By 2000, nervous industry executives were looking into a nearly empty pipeline and decided to dedicate millions of dollars to finding more innovative drugs.

They invested in robotic drug testing kits, but failed to improve their success rate.

And companies, euphoric over the sequencing of the human genome, hired "genomics" teams, hoping to usher in an era of personalized medicine. Many have since scaled back those operations mainly because they don't know how to adapt their mass-market methods to products targeting small groups.

Some industry insiders say such research investment is nothing more than an attempt to impress investors.

"There's a tendency for big companies to play by a scorecard," said Tuan Ha-Ngoc, chief executive of GenPath Pharmaceuticals, a biotech based in Cambridge, Mass. "Sometimes, they move things along too quickly. I'm worried many have sacrificed quality for quantity."

And then there are times when companies kill off viable drugs late in the game for economic reasons. It's an industrywide practice, said Ken Kaitin at Tufts University.

For example, last September Bristol-Myers Squibb discontinued for "commercial reasons" a closely watched diabetes treatment, according to Thomson CenterWatch, which tracks clinical trials.

Earlier this month, Enzon Pharmaceuticals of Bridgewater halted work on an anti-cancer compound after analyzing Phase 2 data and deciding the financial risks weren't worth it, according to a spokesman.

Drugs for several types of cancers, and a variety of diseases, including sickle cell anemia and Crohn's disease, have been scrapped by prominent companies for similar economic reasons. In effect, product development is moving toward an all-or-nothing approach in many labs.

The numbers of drug candidates successfully making it through the lengthy development process would seem to indicate just that. Last year, companies submitted 28 drug candidates for FDA review, not much higher than the all-time low industry hit in 2002.

Some critics say drug companies also wall themselves off from alternative sources of innovation. Before Daniel Scola Jr., joined the law firm of Hoffmann and Baron as a patent attorney, he worked at Warner-Lambert, which developed the revolutionary cholesterol-lowering drug Lipitor. His job at Warner-Lambert, he said, was to fend off inquiries from the outside for fear they would cause problems with patent applications for company products.

"They won't deal with individuals," he said of the big drug makers.

Individuals like Scola's client, Peter Mueller.

The Princeton neuropsychiatrist believes the drug Meridia can successfully treat such ailments as post-traumatic stress disorder, fibromyalgia and Tourette's syndrome.

He obtained a "use patent" for the pill made by Abbott Pharmaceuticals but cannot persuade the company to scientifically investigate his claims and distribute the drug for these purposes.

"With Meridia, our focus is on obesity," said Laureen Cassidy, an Abbott spokeswoman.

At weekly Friday clinics in his office, Mueller offers free help to mental patients, many from out of state, and often dispenses Meridia as an off-label use for their ills. "Unfortunately, the drug companies are afflicted with the NIH syndrome, which stands for 'not invented here'," Mueller said. "It's a tragedy."

As a result, the biggest drug makers may come to resemble a Hollywood studio that doesn't make many of its own films, but instead acquires and distributes sure hits created by smaller players. It's the reason Pfizer — the largest drug company in the world — bought Warner-Lambert.

"Many companies are going to change," said Michael Ferrante, a director in the pharmaceutical research and development practice at PriceWaterhouseCoopers, the consulting firm. "Some are choosing to become marketing machines. They'll divest all basic research and hold onto only late-stage development and marketing."

In effect, they'll be closing their pipelines all together.

Or some, like Merck, which has always hinged its corporate image on its research excellence, will find ways to improve the odds of picking the right drugs. Right now the company is betting big on computer programs that can predict if a person is a good candidate for a particular drug or clinical trial.

"The entire industry has been caught up in a constrained definition of innovation," said Roger Longman, editor of In Vivo, an industry trade magazine. "They've spent a great deal of effort looking for new molecules to treat new diseases, but ignored opportunities for existing molecules. The issue is where are they looking for innovation?"

Regardless of where companies look, analysts such as Patricia Reilly of Life Science Insights, a consulting firm, are growing more convinced that "the blockbuster era is coming to an end."

And when it does, Reilly said, "companies are going to have to find new ways to innovate."