

Old Drugs In, New Ones Out

Combining Generics Can Create Powerful Treatments

By ANDREW POLLACK

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Can an antipsychotic drug from the 1950s be paired with a 1980s antibiotic to shrink 21st-century tumors? Might an anticlotting drug help a steroid relieve arthritis? How about a cholesterol treatment and a pain reliever teaming up to tame diabetes?

Alexis Borisy, the pharmaceutical industry's master matchmaker, is betting they can. And if he is right, he may have found a cheap and quick way to develop a new cornucopia of medicines.

Mr. Borisy is the 35-year-old co-founder and chief executive of CombinatoRx, a biotechnology company dedicated to the proposition that two old generic drugs can together make a powerful new medicine, often for an entirely different disease.

It is too early to tell if Mr. Borisy will succeed and, indeed, one of his company's drugs recently failed in a clinical trial.

But with drug makers big and small struggling to fill their product pipelines, other biotechnology companies are also betting that pairing old drugs can be a better business than inventing new ones from scratch — which can take years and cost hundreds of millions of dollars, with no guarantee of success.

For example, Pozen, based in Chapel Hill, N.C., is developing combination drugs in partnerships with the pharmaceutical giants GlaxoSmithKline and AstraZeneca.

Orexigen Therapeutics of San Diego recently went public based on the prospects for two combination drugs it is developing to treat obesity. And Celator Pharmaceuticals, a privately held company in Princeton, N.J., has raised more than \$40 million from venture capitalists to combine old cancer drugs in a new way.

"We think if we prove this concept clinically we have an almost unlimited pipeline," said Andrew S. Janoff, the chief executive of Celator.

Helping propel the trend is the growing supply of drugs that have lost patent protection, providing a lode of material to test for newfound potential.



Erik Jacobs for The New York Times

Omar Magid, a screening specialist, in the labs of CombinatoRx, a company dedicated to combining old generic drugs to make new medicines.

Information technology also plays a central role for CombinatoRx (which is pronounced com-bin-a-TOR-ics, as in the mathematics field that deals with combinations). The company relies on the latest robotic drug-screening technology and software to test several thousand pairs of medicines a day.

At its laboratory here, researchers and robots systematically pair about 2,000 generic drugs with each other; some 2 million different combinations are possible. Each is tested on human cells. If a drug pair inhibits the cells' production of inflammatory proteins, for example, that might be reason to explore whether the combination might work against arthritis.

Mr. Borisy describes it as a "dumb, brute-force, empirical approach" that assumes current knowledge of disease is too limited to predict in advance what combinations might work. The company does, though, give priority to testing pairs it believes have the best chance of working.

Eight of the company's randomly arranged marriages, including drugs for cancer, arthritis and diabetes, have moved into clinical trials — an unusually high number for a company that is only seven years old. Other companies are taking more calculated approaches. Orexigen, in creating its obesity drug Contrave, took a treatment used for drug and alcohol addiction and combined it with an antidepressant sometimes used to help people quit smoking.

Celator, meanwhile, is focusing on drugs that are already used together to treat cancer. But while doctors now generally use the maximum tolerable dose of each drug, Celator says the ratio of the drugs is what matters more. So the company is developing combination products meant to deliver optimal ratios of the drugs to tumors.

Besides being quicker or cheaper to develop than single new drugs, combinations might also be more effective. Scientists have long known that the biochemical pathways involved in disease are complex, with numerous alternate routes. Trying to interfere with disease by blocking a single point can be like trying to keep traffic from reaching downtown Manhattan by closing a single intersection.

That is why doctors routinely use two or more drugs to treat people with cancer, heart disease, H.I.V. infection and other diseases.

But only more recently have pharmaceutical companies decided to do the combination themselves as a way to increase their profit.

Successful combination drugs already on the market include Advair from Glaxo-SmithKline, which pairs two asthma drugs, and Vytorin, which combines cholesterol-lowering drugs from Merck and Schering-Plough that work in different ways.

When they work, combination drugs mean fewer pills to swallow, making it easier for patients to complete a course of treatment — and, as a result, for companies to hit sales targets.

Combination drugs can also let a weaker-selling medication ride the coattails of a stronger drug, or partly shield a product

Creating New Drugs From Old

On the assumption that combining two old drugs to create a new one can be more cost effective than inventing new drugs from scratch, biotechnology companies have developed products that include the ones listed here

| Company | Drug | Ingredients | Development Stage | Comment |
|--------------------------|---|--|--------------------------------------|---|
| AVANIR PHARMA-CEUTICALS | Zenvia for uncontrolled laughing and crying, and diabetes-linked pain. | Dextromethorphan – cough suppressant Quinidine sulfate – treating heart rhythm disturbances | Phase 3 clinical trials | Dextromethorphan curbs certain neural activities. The quinidine makes the dextromethorphan last longer in the body. |
| CELATOR PHARMA-CEUTICALS | CPX-1 for colorectal cancer | Irinotecan – colorectal cancer Floxuridine – gastrointestinal and other cancers | Phase 2 clinical trials | The two drugs are now sometimes given together by doctors to treat colorectal cancer. But doctors often use the highest tolerable dose of each drug. Celator says it has found that a 1:1 ratio of the two drugs is best. It encapsulates the two drugs in fat globules that deliver them in that ratio to the tumor. |
| COMBINATORX | CRx-102 for rheumatoid arthritis and osteoarthritis | Prednisolone – steroid used for many inflammatory diseases Dipyridamole – blood clot prevention | Phase 2 clinical trials | Steroids like prednisolone can be used to treat arthritis but have bad side effects. The dipyridamole appears to amplify the steroid's desirable effects, allowing only small amounts to be used and reducing side effects. |
| NITROMED | BIDI for heart failure in African-Americans | Isoorbide dinitrate – angina Hydralazine hydrochloride – hypertension | On market | Sales of the drug have been poor; the company says many insurers did not pay for it at first. The company is also fighting the perception that doctors can prescribe the two ingredients separately and get the same effect for less cost. |
| OREXIGEN | Contrave for obesity | Naltrexone – opioid addiction and alcoholism Bupropion – depression and nicotine addiction | Phase 3 clinical trials | Bupropion blocks appetite and other cravings, but it also causes release of brain chemicals that put a brake on that effect. Naltrexone blocks the brake, allowing the appetite suppression to last longer. |
| POZEN | Trexima for migraine headaches | Sumatriptan – migraines Naproxen – pain, fever, inflammation | Awaiting F.D.A. decision on approval | Sumatriptan is GlaxoSmithKline's migraine drug Imitrex. Naproxen is sold as Aleve and under other names. The combination is said to offer longer relief from migraines than Imitrex alone. Being developed with GlaxoSmithKline. |
| VIVUS | Qnexa for obesity | Phentermine – appetite suppression Topiramate – migraine prevention and epilepsy treatment | Phase 2 completed | Topiramate has a side effect that seems to make people feel full. Phentermine is the part of the old fen-phen diet drug combination that remains on the market. |

Source: the companies

The New York Times

that has lost patent protection from generic competition. One of the ingredients in Vytorin, for instance, is Merck's Zocor, which has gone off patent.

But for companies like CombinatoRx, which do not have any drugs of their own, finding value in off-patent products is the whole point.

Mr. Borisy, who dropped out of a Harvard chemistry doctoral program to become a drug industry consultant, started CombinatoRx in 2000 with three researchers from his former Harvard laboratory.

The company's approach to drug research has attracted considerable attention, including Mr. Borisy being named 2003 "innovator of the year" among people under 35 by the Massachusetts Institute of Technology's magazine *Technology Review*. The company has raised nearly \$200 million from investors, including \$44 million from its initial public offering in November 2005.

Several disease foundations have paid CombinatoRx to try to find combinations for treating their specialties. And Angiotech Pharmaceuticals, the company that supplies the drug used in Boston Scientific's drug-coated stent for coronary arteries, has found combinations it hopes to use in future stents.

"They were far ahead of anyone else, and the way they were doing it we thought was just elegant," said Dr. Rui Avelar, the chief medical officer for Angiotech.

For all the company's promise and attention, though, it is far from clear that

any of CombinatoRx's drugs will reach the market. Three of the eight drugs that made it to clinical trials have since been dropped because they did not work well enough in people, despite their effectiveness in the cell-based laboratory tests.

A cheaper way to new treatments, but there may be risks.

Those cold clinical realities have helped pull the company's shares to the \$6 range, below the initial public offering price of \$7 and well under a high of almost \$14 in early 2006.

Currently, the company's lead drug is a treatment for rheumatoid arthritis and osteoarthritis that combines prednisolone, a steroid, and dipyridamole, a blood anticoagulant.

Steroids are used to treat arthritis, but they have undesirable side effects. Adding an anticoagulant seems somehow to amplify the steroid's desirable effects, allowing use of a very low dose with greatly reduced side effects, Mr. Borisy said. The drug has shown promise in early clinical trials.

Combinations of existing drugs can enter clinical trials more quickly than totally new medicines because much is already known about their toxicity and how they behave in the body.

But some industry executives say the combinations risk encountering regulatory problems downstream. They say the Food and Drug Administration must be persuaded that a combination offers a real benefit to patients and is not just a commercial gimmick, because each additional drug a patient uses can raise the risk of safety problems, in part from interactions between the drugs.

Another risk for companies as they mine drugs no longer protected by patents is that other companies might try to sell similar combinations. While the combinations themselves can be patented, legal challenges could arise if the combination is deemed too obvious. Mr. Borisy says he is not worried because "our patents are so obviously non-obvious."

Another business risk is that even if a combination pill is protected by patents, doctors might prescribe the two ingredients separately, especially if that would save the patient money.

Pozen, for instance, is developing a combination of the generic pain reliever naproxen with AstraZeneca's popular heartburn remedy Nexium. The idea is that Nexium will protect the stomach from naproxen's potentially ulcer-causing side effects. But many physicians are already prescribing an antacid pill along with a pain killer — and using generic stomach drugs rather than Nexium.

William L. Hodges, chief financial officer of Pozen, contends that his company's combination pill will be more effective than two drugs taken separately. In the Pozen pill, he says, the naproxen is not released until Nexium has already lowered the stomach's acidity.

Assuming companies like Pozen and CombinatoRx can surmount the challenges of two-drug combinations, the next question is whether three drugs might be even better. The answer appears to be yes, but developing trio drugs would be even more difficult.

For a triple combination, the F.D.A. might want evidence that the trio is better than not only the individual parts but also better than any of the possible pairs. Showing that would require huge and costly clinical trials.

But Mr. Borisy says his researchers and robots will be up to the task. "We're going to get to that," he said, "each step in time."

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