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Early warning system for drug dangers sought

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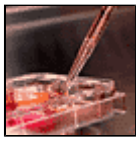

If one company's disaster can transform an industry, the withdrawal of Merck's $2.5 billion painkiller Vioxx in 2004 may become the textbook example.

Primarily, the removal of Vioxx from the market due to heart risks spurred a sweeping examination of the pharmaceutical industry and its regulation. But it also enriched the soil for a new generation of companies trying to update technology that detects whether new drugs may be harmful to the heart.

Vioxx's failure trained a spotlight on the heart as a possible trouble spot for drugs, even though other side effects are more common causes behind sidelined medicines. New companies hoping to meet the need for better cardiovascular-risk detection include VistaGen Therapeutics Inc. of South San Francisco, Perlegen Sciences of Mountain View and Singulex Inc. of Alameda.

A dish of beating heart cells at VistaGen may someday reveal whether a promising experimental drug would actually cause heart attacks. Singulex and Perlegen may identify patients whose cardiovascular health would be hurt by a drug most people can take without fear. The interest in such screening systems has only increased in the past few years.

Vioxx was the most high-profile example among a series of drugs that have been linked to cardiovascular risks, even though the medicines were not designed to have any effect on the heart or blood vessels. That roster now includes the diabetes drug Avandia, certain chemotherapy agents, hormone replacement therapies for menopause symptoms, and some of the newest cancer drugs. Because cardiovascular risks may be life-threatening, they can erode drug sales even if the medicine remains on the market. And the potential risk could boost the cost of drug development.

Calculating risks

Drug regulators are mulling whether larger clinical trials should be required to ferret out heart risks in experimental drugs, no matter what disease they aim to treat, said Dr. Robert Temple, director of medical policy at the Food and Drug Administration. "I think there's an increased appreciation that a non-cardiovascular drug might have an adverse effect" on the cardiovascular system, he said.

But the FDA is also eager to see new technologies that serve as an early warning of unexpected

heart risks, Temple said. VistaGen is developing drug toxicity tests using human heart cells derived from embryonic stem cells, a versatile cell type that can transform into any of the specialized cells of the human body. The heart cells, which beat in time in a culture dish, change their contraction rates when exposed to certain drugs dangerous to the heart, said VistaGen chief executive Ralph Snodgrass.

Singulex is refining a sensitive blood test that can detect single molecules of a protein associated with the death of heart muscle cells in humans and animals. Such tests could flag harmful experimental drugs, and could also identify patients whose hearts are already so weakened that they should take lower doses of certain medicines or avoid them, said Singulex chief executive Philippe Goix.

Avoiding loss

Early screening tests, if validated, would not only protect patients but might also spare drug developers enormous losses. The sooner drug developers know an experimental drug can be harmful, the less money might be wasted on its development. Estimates of the cost of bringing a single new drug to market range from $800 million to more than $1 billion.

In the case of Vioxx and some other drugs, the cardiovascular danger was not fully evident until after the drugs were approved and had been taken by millions of people. Watchdog groups accused Merck of ignoring earlier signals of Vioxx's risks, and patients who had heart attacks or strokes sued the company. Without admitting wrongdoing, Merck offered $4.85 billion to settle most of the suits.

Better risk-detection tests will reduce drug development costs only if manufacturers act on the results by abandoning unsafe drug candidates. But there can be dangers in relying on early tests to jettison experimental drugs, experts say. Screening tests in animals, for example, might eliminate drugs that actually won't cause problems in humans. On the other hand, tests can provide false assurance that a drug is safe, said UCSF cardiologist Dr. Rita Redberg. "Clinical trials take time and they're expensive, but I think there is no substitute," she said.

Dr. Garret FitzGerald, a professor at the University of Pennsylvania School of Medicine who predicted Vioxx's heart risks in 1999 based on knowledge of its mechanism, said a range of tactics should be used to assess side effects. Each tool - lab toxicity tests, clinical trials and studies of drug modes of action - provides part of the picture, he said. "It's just like in a criminal trial - you put together different bits of inconclusive evidence," FitzGerald said.

At this point, the early tools for detecting heart risks are well behind the technology available to test drugs for liver toxicity, a problem that has been intensely studied because it's the main reason for drug withdrawals, Temple said. "I don't think we have that for cardiac problems yet," he said.

Tests used for decades

Many of the current screening methods for cardiovascular risks have been used for decades. Experimental drugs can be tested in animals and in cell cultures before clinical trials in humans begin.

Once trials start, subjects are routinely tested for changes in blood pressure, electrocardiogram patterns, and levels of fats, sugars and other molecules, Temple said. But those methods only work when the drug effect is something the tests can measure.

Some cardiovascular harm occurs by a route that remains mysterious, as in the case of Avandia. "You can't screen if you don't even have a clue as to the mechanism," said cardiologist Eric Topol, chief academic officer for Scripps Health in San Diego.

Dangers to heart

The delicate pumping machinery of the heart is vulnerable to damage that starts elsewhere in the body, said Dr. Bryan Walser, chief executive at Perlegen. The clumping of blood cells in an artery can block the flow of blood and oxygen to the heart, causing the death of heart muscle tissue, Walser said. The heart can also be strained by the buildup of fluids called edema, which may be related to kidney function, he said. Perlegen is looking for human genetic variations that might predict bad reactions to Avandia.

Some drugs, including Avandia and Vioxx, may only carry dangers for a fraction of the population. This is why heart risks can remain hidden during clinical trials in a few thousand subjects, only to emerge once the drug is approved and prescribed for millions of people. Without any clear means of identifying susceptible patients, a drug's use is often restricted even if only 1 percent of the population would be harmed.

"One percent of 20 million people is a lot of people," said Topol. Perlegen is hoping to develop a genetic test to identify patients who should not take Avandia. That method of risk reduction is part of an approach known as personalized medicine.

Until cardiovascular risk screening improves, the burden is likely to fall on pharmaceutical companies to conduct larger clinical trials. Study populations may need to be as large as 12,000 people to uncover a drug's threat to small subsets of the population, said Temple. Such big trials may also be the only means to detect relatively small increases in cardiovascular risks to an individual, he said. Increases of 20 or 30 percent are important because they may add enough to a patient's existing risk to trigger a heart attack or other serious event, Temple said.

Shortcuts to the discovery of drug risks will come from a deeper understanding of genetic variations that amplify cardiovascular risks in some people, say experts including Topol and

FitzGerald. Prescribing would then be guided by each individual's personal risk profile. The current low rate of new drug approvals could rise if drugmakers had tools to match the right patients with an experimental treatment, FitzGerald said.

"The way out of this is personalized medicine," he said.

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