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Need a drug approved? Find a good test

NEW YORK

Manufacturers pressed for tools to help match products and patients

BY ANDREW POLLACK

ChemGenex Pharmaceuticals found out the hard way how important it is to have a trustworthy companion.

Last year, the U.S. Food and Drug Administration rejected the company's drug to treat a subset of leukemia patients whose tumors had a particular genetic mutation. The main problem was not the drug itself, the agency said. Rather, ChemGenex had not specified a companion test that could reliably detect the mutation so that the drug could be given to the patients it was intended to help.

These days, it is often not enough for pharmaceutical companies simply to move a drug to market.

Regulators and insurers are also prodding the companies to develop tests to pinpoint which patients are most likely to benefit from a drug, thereby sparing other patients from needless side effects and expense.

The pressure has thrust drug and diagnostics companies into sometimes awkward partnerships aimed at developing such tests, which are called companion diagnostics. There were at least 25 such deals in 2010 and 15 in the first half of 2011, up from only seven in 2008, according to PricewaterhouseCoopers, a consulting firm.

"The tests are becoming almost gatekeepers to the drug," said M. Trevor Page, director of business development at Dako, a Danish diagnostics company.

The F.D.A. issued guidance to the industry on companion diagnostics in July, including its preference for having the test ready for approval at the same time as the drug. The following month, as if to show how it should be done, it approved two drugs and their accompanying tests.

One of the drugs, Xalkori for lung cancer, from Pfizer, works wonders — but only for the 5 percent of patients whose tumors have a particular chromosomal abnormality, as determined by a test from Abbott Laboratories.

The other drug, Zelboraf, from Roche and Plexxikon, can also produce remarkable improvements, but only for the about half of melanoma patients whose tumors have a particular mutation. The F.D.A. approved a test from Roche's diagnostics division to detect that mutation.

But the simultaneous approval of new drugs and tests is still rare. Before August, the only other dual approval was of Genentech's breast cancer drug Herceptin and Dako's test for the related HER2 protein in 1998. There are more than 70 other tests that guide drug use in some way, according to the Personalized Medicine Coalition, but they are rarely required and often are developed well after the drug reaches the market.

There are numerous economic, scientific and regulatory obstacles to developing companion diagnostics, executives and analysts say.

Often, scientists simply do not know what to test for to predict a drug's effectiveness, or they do not find out until near the end of the drug's clinical trials. And coordinating development and approval of a drug and a test — by two separate companies reviewed by two F.D.A. divisions — can raise the cost of drug development if not done well.

"This is like trying to choreograph a dance," said Dr. Mace L. Rothenberg, who runs cancer clinical trials for Pfizer.

Moreover, it is often a dance between a giant and a pixie, locked in an embrace but with a tendency to move in opposite directions.

Pharmaceutical companies can spend hundreds of millions of dollars to develop a drug, then can reap billions of dollars a year in sales with high profit margins. Diagnostic companies typically spend several million dollars to develop a test, with annual revenue also around that level, and low profit margins.

"You are really trying to get two very disparate industries to understand each other," said Mollie Roth, chief operating officer of Diaceutics, a consulting firm specializing in companion diagnostics.

For pharmaceutical companies, the risk is that a test can lower sales of their drugs by restricting use to a fraction of potential patients.

An often-cited example of such a problem involved Selzentry, a Pfizer drug approved in 2007 to treat people with a certain subtype of H.I.V., the virus linked to AIDS. The test of a patient's virus, offered by Monogram Biosciences, cost about $2,000, and all samples had to be sent to Monogram's laboratory in California. Analysts say the cost and inconvenience of the testing deterred use of Selzentry, especially since it was competing with drugs that could be used by all patients, with no need for testing.

"Top management still sees companion diagnostics as an obstacle between their product and the market," said Jorge Leon, a consultant to both drug and diagnostic companies.

Still, drug companies are embracing companion diagnostics because of pressures to control health spending. Also, in the rare cases where a test is available early in the drug's development, as

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was the case with Xalkori and Zelboraf, clinical trials can be made smaller and less costly by restricting them to patients who are most likely to benefit from the drug.

For diagnostic companies, there is a risk of developing a test in advance for a drug that may never reach the market.

For that reason, drug companies often have to pay all or part of the costs of developing the test. Pfizer, for instance, paid for Abbott to develop the companion test for Xalkori, said Stafford O'Kelly, president of Abbott's molecular diagnostics division.

He said that when it became evident that the F.D.A. would make a decision on Xalkori earlier than expected, Abbott had to work nights and weekends to get the test ready. "Rule No. 1 is that the diagnostic can never slow down the development of the therapeutic," he said.

Companion diagnostic developers have been pushing to share more in the bounty of a successful drug, perhaps via royalties on sales of the drug. But drug companies have resisted this.

"The value is in the combination, so why should one company get all the value?" said Mark R. Trusheim, an executive in residence at the Massachusetts Institute of Technology Sloan School of Management, who has studied the economics of companion diagnostics.

One reason the diagnostic companies do less well, Mr. Trusheim said, is that while drugs typically have market exclusivity because of patents and laws, tests often face instant competition.

Some laboratories at cancer hospitals, for instance, already have their own tests for the melanoma mutation that governs use of Zelboraf and are reluctant to switch to the approved test, which might be less convenient or more costly. Tests developed by a lab for its own use typically do not require F.D.A. approval.

To protect their investments, some developers of companion diagnostics want the name of the test to be specified in the label of the drug, arguing in part that unapproved tests might not be as accurate. Some pathologists oppose this.

The F.D.A. has so far taken a middle ground. The labels for Zelboraf and Xalkori state that an F.D.A.-approved test should be used. But they do not name the test, leaving open the possibility that additional tests can be approved.

Plexxikon, one of the developers of Zelboraf, said in comments submitted to the F.D.A. that linking a drug to a single approved test could allow a diagnostic company "to hold the entire drug development program hostage."

Plexxikon, which is owned by Daiichi Sankyo of Japan, is developing a drug aimed at a type of leukemia with a particular mutation. K. Peter Hirth, the Plexxikon chief executive, said a company holding exclusive patent rights on the test for the mutation was "demanding incredibly high dollars in terms of upfront payments and support, which is prohibitive."

Jeffrey E. Miller, chief executive of the company in question, Invivoscribe, said his company's charges were reasonable considering the possible consequences of not having a validated companion test.

"The cost of developing the companion diagnostic," he said, "is trivial compared to the cost of a failed drug."

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HEIDI SCHUMANN FOR THE NEW YORK TIMES

Officials of the drug maker Plexxikon, using 3-D glasses to view molecular structures. The company has expressed concerns about linking of drug approvals to diagnostic tests.