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Talk of Bird Flu Pandemic Revives Interest in Passed-Over Drugs

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By ANDREW POLLACK

BIRMINGHAM, AL Oct. 7 - Three years ago BioCryst Pharmaceuticals gave up on a drug it was developing to treat influenza.

The drug, peramivir, had failed in clinical trials, in part because not enough of it got into the bloodstream when taken orally. Johnson & Johnson pulled out of a partnership with BioCryst in 2001 when it saw that other flu drugs were not selling well.

But now, amid growing fears of a global bird flu pandemic, peramivir may be resurrected. Scientists using government funds are already testing the drug in animals, this time in a form that is given intravenously or injected.

"We never even thought of the prospect of resurrecting it until avian flu came along," said Charles E. Bugg, chief executive of BioCryst, which is based in Birmingham, Ala. Although the drug is nowhere near formal approval by the Food and Drug Administration, Mr. Bugg said peramivir could be quickly manufactured on an emergency basis for government stockpiles.

But experts say that previous inattention to flu drugs has the world facing a potential shortage that could leave millions of people dead if avian flu were to break out in the next year or two.

After years of lackluster sales -- and, as a result, limited production -- two flu drugs on the market, Tamiflu from Roche and Relenza from GlaxoSmithKline, are in intense demand by governments building stockpiles against a possible bird flu pandemic. Neither company is now in a position to come close to meeting the global demand for their drugs.

A Japanese company, Sankyo, has developed an advanced version of Relenza that did not go beyond early clinical trials but that now, in part with money from Washington, is being studied as a possible avian flu treatment.

"You have to play catch-up in development," said Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases.

The strain of avian flu that has killed birds in Asia has already resulted in the deaths of at least 60 people, most of whom were thought to have had direct contact with infected poultry. But experts theorize that the strain, known as H5N1, could kill millions if it mutated into a form easily passed from person to person.

Such fears were heightened by the finding announced by scientists this week that the 1918 influenza virus that killed as many as 50 million people worldwide was a bird flu that jumped to human beings.

Tamiflu and Relenza failed to sell well as conventional flu treatments because patients and their doctors tend to rely on preventing influenza through yearly vaccines rather than waiting to use drugs to treat the illness. But it could take years before there is an adequate supply of vaccine against bird flu, and so health authorities are counting on antiviral drugs like Tamiflu as the first line of defense after someone has become ill or been exposed to the disease.

The slow sales had prompted Roche and Glaxo to scale back their efforts in promoting and producing Tamiflu and Relenza. And other drugs in development were put on the back burner.

"It's basically the corporate model working," said Arnold Monto, a flu expert at the University of Michigan. "You put your money where the blockbusters are."

Jeremy Carver, chief executive of the International Consortium on Antivirals, a group of scientists based mainly in Canada, said he had identified five drugs that showed some effectiveness against conventional flu in academic laboratories but never advanced because of a lack of commercial interest. He said his group was trying to raise $60 million from governments to move the drugs forward, though it would take years for any of them to reach the market.

And because even now, an avian flu epidemic is still only hypothetical, companies have been reluctant to invest for that alone.

The smaller companies that originally developed Tamiflu and Relenza, and receive royalties on their sales, have accused Roche and Glaxo of neglecting the drugs, contributing to the current shortage.

Tamiflu's inventor, Gilead Sciences, a California biotechnology company, told Roche in June that it wanted to take back the rights to the drug, accusing Roche of a "consistent record of inactivity and neglect" since the medicine was approved by the F.D.A. in 1999.

A Roche spokesman, Terence J. Hurley, said the company had fulfilled all its obligations to Gilead to promote and manufacture the drug and the dispute was in arbitration.

Mr. Hurley said Roche had quadrupled manufacturing capacity in the last two years and would expand it further next year. While the drug is now produced in factories in Europe, Roche is about to add capacity in the United States; American officials have been concerned that a flu outbreak on a wide scale might cause other nations to restrict exports of the drug.

But the Tamiflu production process takes 10 to 12 months. So the company cannot immediately supply the millions of doses being ordered by 40 countries for use in case of a flu pandemic. Mr. Hurley said Roche would make enough Tamiflu this year to treat tens of millions of people, but would not be more specific.

Sales of Tamiflu soared to about $450 million in the first six months of 2005, more than four times those in the period a year earlier.

The United States government has acquired enough Tamiflu to treat 2.3 million people -- each person would take 10 capsules over five days -- and it plans to buy enough to treat two million more people this year.

The government's current goal is to stockpile enough to treat 20 million, and that goal is expected to be raised. Neither Roche nor government officials, though, would say how soon such quantities could be supplied.

With Tamiflu, also known as oseltamivir, in short supply, some attention is turning toward Relenza, which is also known as zanamivir. Approved the same year as Tamiflu, Relenza has been a distant also-ran.

Unlike Tamiflu, which is taken orally, Relenza requires an inhaler. Within months of Relenza's approval, there were instances of respiratory problems and fatalities in users who had asthma or other pulmonary diseases. But some experts say that the inconvenience of an inhaler and the risk of side effects were minor considerations compared with the dangers from flu on a wide scale.

The federal government recently purchased 84,300 treatment courses of Relenza for $2.8 million. Germany recently ordered 1.7 million units. The German order alone exceeded the total amount of Relenza sold worldwide in the last four years, said Peter Molloy, chief executive of Biota, the company that invented Relenza and licensed it to Glaxo.

Biota, which is based in Australia, filed a lawsuit there against Glaxo last year, saying it did not adequately try to market Relenza. After the drug's first year on sale, "essentially all promotion was stopped," Mr. Molloy said.

Biota is seeking about $300 million in royalties it says it would have earned if Glaxo had done an adequate job. (Biota has now teamed up with Sankyo to move Sankyo's version of Relenza forward under a $5.6 million grant from the National Institutes of Health in the United States.) Glaxo denies Biota's accusations in the case, which is headed toward arbitration later this year.

"We lost a lot of money, quite frankly, promoting it, and the demand wasn't there," said David Stout, Glaxo's president for pharmaceutical operations. Mr. Stout said Glaxo was now getting calls from many governments asking about the drug and was stepping up its production capacity. But, he said, "This is not something you can just turn on the faucet and something comes out."

A spokeswoman for Glaxo, declining to cite specific figures, said all the company's supply for 2005 and 2006 was alreadycommitted to health authorities. She said Glaxo planned to apply this year for approval in the United States and Europe to use Relenza both to prevent flu and to treat it. Tamiflu is approved for both uses.

How well the flu drugs would work in the event of a pandemic is still open to question. Experts say that with conventional flu, Tamiflu has been shown to significantly reduce hospitalizations and serious complications like pneumonia, which could lower the death rate if it worked the same way for avian flu. "This is not just a treatment that reduces symptoms," said Frederick Hayden, a flu expert at the University of Virginia.

The drugs might also be taken to prevent flu in those who think they have been exposed to the virus or are likely to be exposed. But such prophylactic use usually requires more of the drug than does treatment for the disease.

Animal and test-tube studies have shown both Tamiflu and Relenza to work against the H5N1 strain of bird flu. Tamiflu has also been used to treat people infected with H5N1 in Asia, with only mixed success -- though in some cases, treatment might have been started too late.

BioCryst's drug, peramivir, has also shown effectiveness against some strains of avian flu in mice. When peramivir, Tamiflu and Relenza are all given by injection, "peramivir is definitely better," said Robert W. Sidwell, a professor of virology at Utah State who is testing various avian flu drugs for the National Institutes of Health. Dr. Sidwell has been a consultant to BioCryst.

Concerns about avian flu have helped BioCryst's stock, which closed yesterday at $10.26, more than double in the last three months.

Dr. Bugg, BioCryst's chief executive, said the N.I.H. was expected to begin safety tests of peramivir in people this winter and could test its effectiveness next year in Southeast Asia.

Johnson & Johnson and BioCryst had decided that an injected drug would never be able to compete with Tamiflu as a treatment for conventional flu. But in a pandemic, people might not mind getting a shot. And an injected drug gets into the bloodstream more quickly than a pill.

Dr. Bugg said peramivir would also be far easier and cheaper to produce than Tamiflu. He said a contract manufacturer in Switzerland could quickly make enough of it for eight million people, using precursors that Johnson & Johnson had made before it abandoned the drug.

It would take $10 million and six to nine months, he said, for the manufacturer to scale up to make 10 million treatments a month -- which is thought to be more than Roche can make of Tamiflu. Because of the limited commercial prospects for the drug, Dr. Bugg said he hoped that governments would come up with that $10 million.

"It's kind of hard to have our investors step up to the plate," he said, "when it's still not clear what the commercial potential is."

Photo: Shane Arnold researching peramivir for BioCryst in Birmingham, Ala. (Photo by Dana Mixer for The New York Times)(pg. C1); A vial of the flu drug peramivir in injectable form at a BioCryst lab. (Photo by Dana Mixer for The New York Times)(pg. C4)

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