PCR ENZYME

The More You Use, the Cheaper It Gets

Big users of the polymerase chain reaction (PCR) got some good news last month when the Swiss-based drug company Hoffmann-LaRoche agreed to give them a discount on the price of the key enzyme needed to carry out the revolutionary DNA amplifying technique. But Roche's announcement has left some researchers complaining that the company's prices will still take too big a bite out of their grants.

PCR has become an essential tool for genome researchers, but Roche, which holds patents on both the process and the enzyme, known as Taq polymerase, has maintained the price of the enzyme at a level that has angered many researchers. Currently, large-scale users pay around 50 cents a unit for Roche's Taq, which is marketed by the Perkin Elmer Corp. That can add up to hundreds of thousands of dollars a year for some labs. Under the new scheme, however, Perkin Elmer will offer the enzyme to major centers at less than half that price.

Specifically, labs ordering more than 250,000 units of Perkin Elmer Taq a year will pay 24 cents a unit. Beyond that, a sliding price scale will operate, dropping to 18 cents a unit for centers buying more than 5 million units a year. Some large genome centers will get an even better deal, worked out between Roche and officials from the Human Genome Project: 17 genome centers funded by the National Institutes of Health and three Department of Energy centers will receive one unit free for every one they pay for, so long as they purchase at least 250,000 per year.

Although the new prices currently apply only to U.S. labs, "we are planning to offer similar programs outside the United States," says Perkin Elmer spokeswoman Julianne Grace. She adds, however, that the discounts will not be available to smaller labs that might think of grouping together into a "buyers' club" to order collectively more than 250,000 units of enzyme a year. (In a separate move to open up the PCR market, Roche has also in the past few weeks licensed the German company Boehringer Mannheim to sell its Taq for use in PCR.)

For many of the U.S. Human Genome Project's large gene mapping and sequencing centers, the bulk purchase program and "matching grants" of free Taq will bring major savings. The Baylor College of Medicine sequencing center, for instance, will see its Taq bill drop from about $240,000 to $60,000. The percentage savings will not be so great for all the genome centers, however. Several expect to use only marginally more than 250,000 units of Taq, so doubling up with 250,000 free enzymes is not much of a benefit for them; and some centers currently use cheaper Taq supplied by companies other than Perkin Elmer—at the risk of legal action, because Roche maintains that this breaches its PCR patents. Francis Collins, director of the National Center for Human Genome Research, accepts that the old Perkin Elmer prices were forcing people "to do things that were possibly improper." But he is confident that the new deal will encourage major genome centers to comply with Roche's patents.

Nevertheless, some PCR users remain extremely critical of Roche. Take molecular geneticist Ronald Sederoff of North Carolina State University, who is running a gene mapping project to develop strategies to improve breeding programs in forestry that will use at least 200,000 units of Taq a year. Since publicly criticizing Roche's stance on Taq earlier this year (*Science*, 12 March, p. 1521), Sederoff has been offered the enzyme by Perkin Elmer at 20 cents a unit. But even this price is "going to bankrupt us," he says.

Sederoff had originally hoped to make his own Taq, but Roche turned down his request for a license to do so. Sederoff calculated he could make Taq worth $10 million at list prices for an outlay of only $1,000—an estimate confirmed by other researchers approached by *Science*. "I'm willing to grant them a 100-fold markup," says Sederoff. But the profits being made by Roche and Perkin Elmer from Taq are excessive, he argues.

Collins sympathizes with the complaints of researchers who, like Sederoff, will not benefit from the deal negotiated for the major genome centers. "We had to start with the highest volume users," he says. "But I am hoping that this will be the beginning of a downward trend." What's needed, Collins suggests, is for individual labs to negotiate hard with Perkin Elmer and Roche to drive down prices. "My perception is that they're willing to deal," he says.

–Peter Aldhous

AIDS DRUGS

Harvard Group Makes a Splash—Twice

Many AIDS researchers raised a skeptical eyebrow last winter, when a flurry of stories appeared in the news media suggesting that an AIDS cure may be just around the corner. The basis for the media frenzy? A paper in the 18 February *Nature* by Yung-Kang Chow, Martin Hirsch, and Richard D'Aquila from Harvard Medical School reporting that a combination of three drugs appeared to be effective in stopping HIV from replicating. The Harvard group also proposed a novel mechanism to explain why the combination worked. Many researchers kept their optimism in check because the work had been done in the test tube and, as some scientific wags pointed out, even gasoline can kill HIV in the test tube. Others attacked the specific data generated by the research as flawed (*Journal of NIH Research*, April, p. 30 and *Science*, 28 May, p. 1258).

The skepticism, it turns out, was thoroughly justified. The Harvard group, based at Massachusetts General Hospital, has conceded that some of its data were flawed—and the media is in a feeding frenzy once again, with a new diet of stories reporting the embarrassing mistake. "It's unfortunate that the whole thing has made a big splash both times," says Nick Short, the biology editor for *Nature*, which received a letter from the Harvard group explaining the error.

The reason the Harvard study attracted so much attention is that it suggested a way around one of the most vexing shortcomings of anti-HIV drugs: The virus inevitably mutates and becomes resistant to all drugs that have so far been tried on it. In the Harvard experiment, the researchers tried to turn that propensity to mutate against the virus; in essence, they tried to make the virus commit a form of hari-kari.

Specifically, the researchers used three drugs that all target the essential HIV enzyme, reverse transcriptase (RT). Their work suggested that the combination of known mutations arising from the three drugs crippled the RT, preventing HIV from replicating. But as the Harvard researchers explain in their letter to *Nature*, which has yet to be scheduled for publication, the new data reveal that they had inadvertently introduced a mutation that had not been triggered by one of the drugs. *Nature*'s Short says the paper went through "considerable revision," adding "there is no way the peer-review system could have spotted the error that was made."

No one from the Harvard group was available for comment last week, but Massachusetts General Hospital released a statement on 22 July noting that the "regrettable" error "does not change...the fact that for whatever reason, as we reported in February, the treatment does work in the test tube." The vague statement did not explain how the test-tube efficacy could remain unchanged. The statement expressed "cautious optimism that the treatment will offer an advance." Human trials with the three drugs—AZT, ddI, and nevirapine—are currently under way at several sites in the United States.

–Jon Cohen