New HIV drugs approved after some deal-making

They worked late into the night hammering out the deal. When it was over, ritonavir, Abbott Laboratories' new HIV protease inhibitor, had been licensed in record time by the Food and Drug Administration for use in all HIV-infected patients. Although it is the second protease inhibitor approved (the first was saquinavir, manufactured by Hoffmann-LaRoche, Inc., which was licensed in December), it was the swiftest approval ever for an AIDS drug — 72 days after the application was submitted — and could in fact be the fastest for any drug in the history of the agency.

But getting there was not as easy as everyone expected. The FDA's Antiviral Drugs Advisory Committee surprised everyone by declining to recommend that the FDA grant approval for widespread indications, urging instead that approval for ritonavir be given only for treating patients in advanced stages of disease. The company had asked for approval for the broad spectrum of HIV infection, starting with the earliest stages of infection. Because the drug's most compelling data involved clinical end points — not surrogate markers — the company had asked for traditional, or full, rather than accelerated approval for the drug. (Accelerated, or conditional, approval means that research on the drug has shown promising surrogate marker data, which may or may not be predictive of clinical end points.) A trial of ritonavir in advanced patients had shown that those taking ritonavir experienced a cumulative mortality rate forty percent less than for those on a placebo, and a fifty percent greater reduction in disease progression than that of the controls.

The problem, however, was that this trial had involved only advanced patients who were already very sick (reminiscent of the same type of studies that quickly catapulted AZT onto the market in 1987), and committee members were reluctant to make the leap beyond indications for that group. Despite research that showed good surrogate marker data but no clinical data for the less advanced group — clear increases in $CD4^+$ T cells and dramatic reductions in viral load — Abbott decided to go for full approval for all indications.

This did not escape the panel, which balked at licensing the drug for any indications beyond the sickest patients. "The criteria for full approval have been met [for the advanced group]," said panel chairman Fred Valentine of the New York University Medical Center. "We have strong surrogate data for the less advanced group. But we don't have an application for that."

The committee argued nearly four hours beyond its scheduled adjournment time about how to resolve this, with some members — particularly those representing the activist community — feeling that the drug should be made available to everyone. The debate was clearly frustrating to officials from both the agency and the company, both of whom had anticipated a swift recommendation from the panel to license for widespread indications.

On several occasions during the marathon session, both FDA Commissioner David A. Kessler and the agency's director of its antivirals decision, David A. Feigal, Jr., tried to steer the panel back on track, explaining the regulatory requirements and how the company could meet them in order to gain full approval. And they pointed out that, without full approval, there could be problems arising from a narrow indication. (Once licensed, of course, a physician can prescribe a drug for anyone. But insurance coverage could be denied those who obtain the drug for "off-label" uses, making ritonavir — at approximately US$6,000 a year — pro-

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ACT-UP/Paris members protest plans to make ritonavir available by lottery.

Protestors say "non" to HIV drug lottery

Before its record approval by the US Food and Drug Administration, a limited amount of the drug ritonavir (the HIV protease inhibitor made by Abbott Laboratories) was available by lottery to patients with advanced AIDS, an arrangement agreed to by AIDS activists and government officials alike. A dramatically different story has emerged in France. A recommendation by the French National AIDS Council (CNS) that lots be drawn to decide which HIV-infected patients could get ritonavir was angrily rejected by the AIDS community, doctors and politicians alike. In response, Prime Minister Alain Juppé took a firm stand against the drawing, temporarily cooling public outrage. The AIDS associations, however, still believe that the government's position is unclear toward the major drug companies' business strategies and the potential shortage their policies might entail.

In early February, following presentation of promising data at the Third Annual Conference on Retroviruses and Opportunistic Infections (*Nature Medicine* **2**, 257; 1996), Abbott asked French authorities to grant Ritonavir a temporary use permit for an initial 100 compassionate treatments, another 1,000 treatments in April, and 1,000 more each month after that. However, 15,000 people in France fit the clinical trial criteria (less than 100 CD4 per cubic milliliter) The AIDS community was particularly outraged because Abbott had just announced that it had enough Ritonavir to supply the entire American market. AIDS activists object to the industry's plan to first corner the US market before supplying the rest of the world — a policy that they say shows little concern for the disease victims.

Another reason the lottery was rejected is because the French feel that doctors rather than luck should be the decision-makers about treatment. "In France, the idea that a patient's care should be handed over to fate is unacceptable," said Franck Fontenay of TRT5, a consortium of five French AIDS associations.

The lack of ritonavir may be ameliorated somewhat by the promised delivery of 3,000 treatments (and more to follow) of indinavir, an HIV protease inhibitor made by Abbott-rival Merck & Co. This should meet the rise in physicians' requests for protease inhibitors, as well as provide incentive to Abbott to supply more of its protease inhibitor to the French market.

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