will push for an expedited review of the NIH patent by the Patent Office. Indeed, one of the few things on which people agree is that lingering uncertainty is bad for industry and bad for international relations. "It could be a real problem if this goes on for a long time," says Henderson.

Meanwhile, another controversy is brewing over the United Kingdom's cDNA project—specifically, over access to their database. Tony Vickers, head of the resource center for the Medical Research Council project, insists that the UK data will be open to academic researchers, though industry will pay a subscription fee. "That is a crock," responds Norton Zinder of Rockefeller University, one of several U.S. scientists who accuse the British of planning to keep their data secret. This new dispute, as well as U.S. scheme, seem certain to be on the agenda at the first of perhaps many congressional hearings on the issue, scheduled for 20 November, 2 days after this issue of *Science* went to press. ■ LESLIE ROBERTS

# FDA Committee Raises AIDS Vaccine Hurdles

A highly charged meeting of a Food and Drug Administration (FDA) advisory committee on 12 November disappointed biotech companies making AIDS vaccines and in the process triggered what some commentators called a "bloodbath" on Wall Street. The vaccines in question, though, aren't the usual suspects. When the subject of AIDS vaccines comes up, most people think of injections for those who are not infected—to prevent them from getting the disease. But one of the main types of AIDS therapies now being considered is the immunotherapeutic vaccine, a vaccine to boost the immune systems of those already infected with HIV. Several companies are now testing such vaccines in human beings and had hoped to market them soon. But the FDA advisory committee, after a sometimes heated debate, moved back the finish line that therapeutic vaccines must cross before going to market.

What stirred up all the trouble during the deliberations of the FDA Vaccines and Related Biological Products Advisory Committee (which consists of outside experts whose decisions are not official but carry weight in the FDA) was the question of what data the companies must show to prove their vaccines work. Actual clinical data showing that patients improve from a particular therapy is hard to come by, because people with HIV infection can remain disease-free for years. In the absence of clinical data, the companies had hoped to use "surrogate endpoints," such as an improvement in the number of CD4 cells, the key white blood cells that are depleted in those infected with HIV. But the committee voted unanimously that even if an experimental vaccine produced an improvement in CD4 counts, that evidence alone should not be grounds for licensing.

The committee members said they were skeptical about CD4 counts as surrogate endpoints because they do not think those numbers can be depended upon. Recent unpublished data from an ongoing clinical trial of the anti-HIV drug AZT indicates the drug can improve clinical outcome independent of CD4 levels. And, as the committee's chair, Richard Johnston Jr., a pediatrics professor at the University of Pennsylvania School of Medicine, puts it, "There is no good evidence to show that if you prop up or stabilize CD4 counts, especially by immunologic means, that it will be beneficial to patients."

Those most immediately affected by the committee's opinion are three companies that have already been given the green light by the FDA to test their vaccines in HIV-infected people. Clinical trials of AIDS vaccines from Connecticut's MicroGeneSys and San Diego's Immune Response Corp. have already shown that their products are safe and can stimulate the immune system; San Francisco's Genentech is just embarking on its first human trial.

The committee came down hardest on MicroGeneSys, which had submitted the proposal that led the FDA to call the meeting. An ongoing, double-blind, randomized trial of the company's vaccine conducted by the U.S. military in 130 patients is planned to last 3 to 5 years. MicroGeneSys had asked the FDA whether the company could file a product license application as early as 9 months into the trial if CD4 counts improved. But biostatistician Thomas Fleming from the University of Washington noted that "we should keep in mind there are substantial negative consequences when you compromise the reliability of conclusions with less rigorous scientific approaches."

Though Genentech's human trials are just beginning, the company's designs for future trials also include relying heavily on CD4 as a surrogate marker. Immune Response, on the other hand, presented a different design, one that some committee members thought could offer a way forward through the "surrogate endpoint" dilemma. Rather than using CD4 levels as a primary surrogate marker, Immune Response's clinical trial in 100 HIV-infected people is assessing its vaccine's effects on virus levels in blood cells. Some committee members suggested that combining such "viral load" data with CD4 counts could provide compelling information. This 1-year trial is planned to end in September, and the company will now likely move up a larger planned trial using clinical endpoints.

The FDA advisory committee's decision sent a strong message that CD4 count alone isn't the appropriate finish line for vaccine trials. Yet, given the urgency of the need for AIDS vaccine and therapies and the complexity of obtaining clinical data, the question of surrogate endpoints isn't about to go away. Indeed, some at the hearing argued that the use of surrogate endpoints is of real benefit to patients, and that surrogate endpoints will certainly continue to be used. Clinical pharmacologist Lewis Sheiner of the University of California, San Francisco, argued that the real question was not doing away with uncertainty, but simply "how much uncertainty we can tolerate." Said Sheiner, "It's not a question of whether we will use surrogate markers—we have and we will."

And FDA representatives at the meeting conceded that positive data based on several surrogate endpoints could lead to approval of a product, as long as the manufacturer agreed to continue gathering clinical data. If the vaccine did not reduce the amount of AIDS-related disease in immunized patients as compared to a control group, the companies would later be required to pull their products from the market.

But Wall Street wasn't mollified. Several stocks dropped, and ironically it was Immune Response, whose trial relies the least heavily on CD4 counts, that took the biggest fall, descending 15 3/4 points the day after the meeting. The financial news show CNBC, on the Financial News Network, described the drop in Immune Response's stock as a "bloodbath." Yet the bloodbath on Wall Street remains a minor affair compared to the one among AIDS patients, and there will no doubt be many further ups and downs in biotech stocks as researchers hunt for what some researchers are calling "vaccine therapy" for infected people. And that is a search in which the question of surrogate endpoints will probably take on increasing prominence. ■ JON COHEN