FDA ADVISORY PANEL

STREPTOKINASE, YES; GENENTECH'S T-PA, NO

WASHINGTON, D.C.—A top advisory panel for the U.S. Food and Drug Administration (FDA) has told the agency to wait for more data before approving Genentech's (South San Francisco, CA) promising clot-dissolving protein, tissue plasminogen activator (t-PA). The recommendation, which surprised many observers and even some FDA officials, is an obvious blow to Genentech, whose stock began plummeting several days before the meeting. In another decision, the advisory panel ironically recommended broader use of a similar but less specific agent, streptokinase, for treating heart attack patients.

The meeting late in May of FDA's advisory committee on cardio-renal drugs, which includes experts drawn from medical centers and teaching hospitals, often crackled with tension. Genentech director of clinical research Elliot Grossbard and Harvard Medical School professor Eugene Braunwald (who is overseeing a nationwide clinical trial of t-PA) sharply disagreed with the FDA committee over the safety and efficacy of the product, which began clinical tests in 1985.

FDA officials and expert panelists questioned whether the drug was safe, suggesting that it caused a high incidence of serious bleeding episodes among heart attack victims treated with it. Grossbard countered that the panel "substantially underestimated" the number of people in the study, thereby inflating the apparent incidence of dangerous side effects. He contends the drug is safe when administered at the proper therapeutic dose, generally 100 milligrams per patient.

"You...find any number you wish...to support whatever opinion you want," responded FDA medical officer Raymond Lipicky, who argued that available clinical data for t-PA are both confusing and inadequate. "The issue of pharmacokinetics is clouded," he added. "[The available information] doesn't make sense."

Braunwald, who filed a disclosure statement with FDA indicating he owns no Genentech stock and receives no personal payments from the company, has studied both streptokinase and t-PA as treatments for acute heart attacks. Indeed, in a parallel study of the two drugs, he and his collaborators found that t-PA was twice as effective, and just as safe, as streptokinase. This t-PA superiority led an ethical review board to drop streptokinase from the clinical trial.

The FDA panel, however, recommended approving streptokinase for treating acute heart attacks, basing its decision in part on a long-term clinical trial in Italy showing that the drug reduces the number of deaths among heart patients. No comparable data are yet available for t-PA because clinical trials began only relatively recently. Although both drugs are widely thought to act by dissolving clots proteolytically, the FDA panel voiced doubts that such a mechanism fully explains streptokinase's action. The panel "only believes it dissolves clots, but is not sure of it," an official said. However, because streptokinase reduced mortality in clinical trials, the panel unanimously approved its wider use. This non-engineered, bacteria-produced product is marketed as "Streptase" by Behringewerke AG (Marburg, F.R.G.) and Hoechst-Roussel Pharmaceuticals (Somerville, NJ), and as "Kabikinase" by KabiVitrum AB (Stockholm).

Although the decision to postpone approval of t-PA came as a surprise, panel members indicated they would probably revise their ruling when more clinical data about the drug become available. "My gut feeling is that t-PA is good, but the real data are not here," said panelist Jeremy Ruskin of Massachusetts General Hospital (Boston). "I am not sure t-PA can ride on the coattails of streptokinase," added Carl Leier of Ohio State University (Columbus). Ultimately, the panel argued that t-PA's known ability to dissolve blood clots, although impressive and similar in that regard to streptokinase, was not enough to approve its use in treating heart disease. Instead, the panel demanded convincing evidence that the experimental drug reduces mortality.

"You may be asking the impossible," Braunwald told the panel. "You have to be careful you're not rejecting a drug that works twice as well [as streptokinase]."

Whether the panel's decision signals a general slowing of genetically engineered pharmaceuticals into the marketplace is not yet clear. Although the panel insisted that t-PA meet more stringent requirements, FDA officials seemed uncertain as to whether this same strict criterion would be applied to other thrombolytic products that several biotechnology companies now have in earlier stages of development.

—Jeffrey L. Fox

STATE FUNDING

ENDOTRONICS' BIOTECH BACKLASH

ST. PAUL, Minn.—The upheaval at Endotronics this spring (see *Bio/Technology* **5**:433, May '87) nearly quashed an ambitious biotechnology initiative in Minnesota. Although the Coon Rapids, MN-based company's problems were separate from the state's comprehensive four-year plan for biotechnology, the well-publicized debacle so stirred public opinion and embarrassed state officials that they were on the verge of tossing out the good with the bad.

As a reform measure, Minnesota legislators have passed a new law mandating comprehensive review of state-funded science and technology program initiatives. This should provide state officials with expert advice, peer evaluations, economic analysis, and follow-up data on all projects receiving state support. The standing 13-member advisory committee, which includes representatives from universities and industry under the direction of a scientist, will be part of a new state office of science and technology.

The new program represents "an important resource for the state," says Marilyn Bach, the former executive director of the Minnesota Council on Biotechnology (MCB), which has had its functions absorbed by the new state office. Back in 1984, the governor appointed a task force that led the next year to the legislatively established MCB.

MCB's four-year plan outlined how the state could support—and benefit from—this emerging technology. It had been well received until the Endotronics affair provoked widespread skepticism and put it in jeopardy during the final days of this year's legislative session. Last-minute persuasion, however, helped restore waning enthusiasm for the biotech proposals, reinstate budgets for at least some programs at the University of Minnesota, and postpone action on several other components, including plans for training high school teachers.

—JLF