DATELINE/

VALUATION DROPS $1.5 BILLION

FDA SETBACK FLATTENS CENTOCOR

NEW YORK—Oftentimes, as a biotechnology company's lead product goes, so goes the company. Last year, for instance, Cetus (Emeryville, CA) merged with its neighbor Chiron after an advisory committee of the U.S. Food and Drug Administration (FDA, Bethesda, MD) failed to recommend its flagship product, interleukin-2 (IL-2), for approval to treat kidney cancer. Along with battering Cetus's stock, the rejection left the company with little hope of staunching its annual tide of red ink, as it had based its profit expectations on IL-2 sales.

Centocor (Malvern, PA) hopes to avoid Cetus's fate. On April 15, FDA announced it would not approve Centocor's lead product, Centoxin, despite an FDA advisory committee's recommendation last September to okay it. Centoxin, a human monoclonal antibody, treats gram-negative sepsis, which annually kills 70,000 hospital patients in the U.S. Centocor's stock took an immediate 41-percent beating following the FDA announcement, and since February, when FDA first questioned Centoxin, the company has lost over $1.5 billion in market value. Indeed, Centocor had expected U.S. sales of Centoxin to make it profitable this year, though it lost $196 million last year.

Not for sale

Centocor claims it's not for sale. Rather than rely on Centoxin sales, Centocor now plans to raise badly needed cash by selling marketing rights to some of its products and by offering contract manufacturing at its two monoclonal manufacturing facilities. Previously, Centocor had taken fierce pride in not selling product rights, as it sought to build an independent drug company. Among Centocor monoclonals awaiting FDA approval are a cardiac imaging agent and a blood-clot imaging agent. Products in clinical trials include monoclonals for bacterial infections, clotting disorders, rheumatoid arthritis, and coagulation disorders.

Centocor also announced a management shake up. Its board of directors created an executive committee chaired by Michael Wall, a Centocor founder and former chairman. Wall will work closely with Hubert Schoemaker, the company's chairman and chief executive officer. James Wavle, Centocor's president and chief executive officer, resigned.

Centocor's FDA troubles arose because the company changed its protocol for analyzing Centoxin clinical-trial data after seeing interim results midway through the trial. Peeking at the results, says FDA, could have biased the trial's results. Originally, Centocor set a primary endpoint of survival 14 days after Centoxin treatment. At 14 days, however, an analysis of a subset of 200 patients with gram-negative bacterial infections in the blood showed no statistically significant difference in survival between Centoxin-treated patients and placebo-treated patients.

FDA's refusal of Centoxin caused Centocor to lose $1.5 billion in market value, shake up its management, and plan to raise cash by selling marketing rights to its products.

Following its interim look, though, Centocor added a new primary endpoint of survival 28 days after Centoxin treatment. At 28 days, an analysis of the same 200-patient subset showed that 45 of 95 placebo-treated patients died, while 32 of 105 Centoxin-treated patients died, a difference of "marginal statistical significance," says FDA.

The FDA advisory committee recommended Centoxin approval based on Centocor's 28-day-endpoint analysis. Yet when FDA found out about Centocor's early look, it focused on the company's 14-day-endpoint analysis and decided against Centoxin approval. FDA has asked Centocor to submit "data from an additional well-controlled trial before further consideration" of Centoxin.

Suspect maneuver

"Once FDA finds a suspect maneuver like the one Centocor used in revising its plan, it begins to suspect bias in all the trial procedures. It then holds the data to the highest statistical standards possible for the product to gain approval," says Jeffrey Casdin, a biotech analyst at Oppenheimer (New York).

The setback could mean Centoxin is a "dead product," says R. Brandon Fradd, a Montgomery Securities (San Francisco, CA) biotech analyst. If Centocor must conduct a second phase-III trial on Centoxin, FDA won't likely approve the product before 1995. By then, second-generation products that are more effective against sepsis will have reached the market. Companies developing such products include Chiron, Synergen (Boulder, CO), Immunex (Seattle, WA), and Genentech (S. San Francisco, CA).

Even Centocor admits Centoxin—which costs $3,750 a dose—isn't very effective against sepsis. It estimates that for every 1,000 sepsis patients treated with Centoxin, just 68 lives are saved. This is because, in part, only 50 percent of sepsis cases are caused by gram-negative bacteria, and 40 percent of those cases end in death.

Centoxin is also hamstrung by an ongoing patent dispute with Xoma (Berkeley, CA). Last October a U.S. district court ruled that Centoxin infringed a Xoma patent. And in December the court ordered Centocor to make payments to Xoma on U.S. sales of Centoxin. First-year European sales of Centoxin were disappointing, moreover. Sales in four countries totaled just $8.4 million last year.

Oppenheimer's Casdin believes the clock is ticking on Centocor. "Management will either have to fix the situation with FDA quickly or have the company sold out from under it," he says, adding that by year's end the company's "deteriorating financial situation will begin to compromise its ability to negotiate a sale." —**B.J. Spalding**