# FDA GIVES NOD TO CENTOCOR, PASSES ON XOMA

WASHINGTON, D.C.—Centocor and Xoma brought recent data for similar anti-sepsis monoclonal antibodies before an FDA advisory panel last month. Panel members lukewarmly recommended approving Centocor's Centoxin. However, FDA unexpectedly preempted the committee from deciding on Xoma's E5 by saying the agency was "not prepared to accept a recommendation regarding licensure of this product."

Centoxin and E5 are directed against endotoxin, which is part of the outer membrane of gram-negative bacteria. The release of endotoxin during infections, particularly when bacteria invade the blood stream, can have dire consequences for patients. Symptoms—including kidney failure, respiratory distress, and blood-system abnormalities—can lead to septic shock and death.

The two products have been traveling a similar path of preclinical and clinical testing. Although both are monoclonals, they are made somewhat differently. Xoma's product is made in mice cells, whereas the Centocor antibody is made from cells that are part human and part mouse.

Last October both products were touted for their ability to reduce the number of deaths among patients who developed septic shock. Since then, however, the results from clinical tests of the products look less and less similar, with E5 apparently losing ground to Centoxin. Yet the differences between the products are not entirely clear cut, and direct comparison of Centoxin and E5 is difficult, if not impossible, because the respective clinical trials are designed differently.

"It's possible that a head-on comparison is needed, and that E5 is superior to Centoxin," says Samuel Saks, Xoma's vice president for clinical research. Several panelists and FDA officials agree. Nonetheless, Centocor officials were arguing that their product saved the lives of nearly half of the patients in shock during several clinical trials. Xoma officials, on the other hand, were emphasizing how E5 relieves several symptoms that may lead to septic shock.

Even though the current outlook is unfavorable for E5, all is not lost, cautions advisory-panel acting chairman Richard Johnston, Jr., who is physician-in-chief of Children's Hospital of Philadelphia in Pennsylvania. The FDA certainly created a "confusing situation" for panel members by preempting any decision on E5, he says. But part of the explanation is that Xoma deluged agency officials with new clinical data shortly before the meeting. Perhaps "all the data are there" for making a favorable decision, but they are neither organized nor analyzed adequately yet, Johnston says.

"In some sense, the indications for Centocor's product are fuzzier," Johnston adds. Thus, panel members referred to the clinical finds as "borderline," and only gingerly recommended its use for certain patients, including those presumed to have bacteremia, endotoxemia, or to be in a state of septic shock.

"I came here convinced of a clinical effect, but you are confusing the hell out of me," said consultant Frederick Robbins of Case Western Reserve Medical School (Cleveland, OH) to other members of the panel. Some confusion is inevitable because "the clinical syndrome is messy," he points out. He, other consultants, panel members, and FDA officials seem to share the view that septic shock entails an overlapping series of symptoms. This picture of the disease—or "syndrome," as some committee members prefer to call it—greatly complicates the clinical evaluation of candidate therapies.

Other complications for the products include discrepancies between laboratory and clinical findings, as well as safety and manufacturing considerations and concerns over the projected high cost to patients for using either product. Advisory-panel members are not supposed to consider cost issues. However, when faced with ambiguous clinical findings and a growing recognition that national health-care costs are rapidly climbing, it becomes increasingly difficult to justify recommending high-cost products for FDA approval, a panelist notes. **—Jeffrey L. Fox**

# PRODUCTS CROWD SEPSIS PIPELINE

NEW YORK—With all their limitations, anti-endotoxin monoclonal antibodies leave lots of room for competing approaches to the cascade of events comprising shock. In particular, clinicians seem to want drugs that would counter shock from all types of infection, including gram positive and fungal, as well as gram negative. That means disarming cytokines.

Endotoxins appear early in the shock cascade, eventually triggering the body's production of two troublesome cytokines, tumor necrosis factor (TNF) and interleukin 1 (IL-1). Work on products that neutralize cytokines is under way at Centocor, Xoma, BASF Bioresearch (Ludwigshafen, Germany), Cetus (Emeryville, CA), Chiron (Emeryville, CA), Synergen (Boulder, Co), and Immunex's (Seattle, WA) affiliate Receptech.

BASF Bioresearch, Chiron, and Centocor are all working on anti-TNF monoclonals. Chiron is in Phase-II clinicals with a mouse antibody licensed from Rockefeller University (New York). Bayer's Miles Cutter Biological (Berkeley, CA) is making the drug for Chiron and is conducting Chiron's Phase-II clinicals.

BASF Bioresearch group leader Achim Moeller says his company's Phase-I clinicals in Germany, begun last year, are showing low toxicity. "We think we have a very good antibody," he says, adding that the company plans to pursue approval first in Germany.

Centocor, for its part, is not banking on Centoxin alone but is in Phase-I trials with CenTNF, its anti-TNF monoclonal, and expects to go into Phase II by year end. "There is some evidence to suggest that TNF levels rise before IL-1 and that TNF mediates IL-1," says a Centocor spokesman.

Instead of focusing on monoclonals, Synergen is working on Antril, an IL-1 receptor antagonist. Now in Phase-II clinicals, the company plans to begin a multinational Phase-III study by year end.

Although some analysts have expressed concern that Antril would have to be given in large doses, Synergen says that dose levels haven't been established and that Antril's Phase-II dose-ranging studies show that the drug is safe even at the highest dose given, 10 mg/kg of body weight. "There weren't any side effects at all," asserts a company spokeswoman.

Receptech's mandate is to develop soluble receptor products for a variety of cytokines, including TNF and IL-1. The company anticipates starting Phase-I clinicals this year.

And whatever FDA decides on E5, Xoma at least has another iron in the anti-sepsis fire. The company has licensed bactericidal permeability increasing (BPI) protein, an antibacterial protein. Xoma president Patrick Scannon claims that BPI, a recombinant human protein, shows antibacterial activity, binds and neutralizes endotoxin, and has "strong anti-cytokine properties" against TNF, IL-1, IL-6, and IL-8. Xoma hopes to begin trials next year. **—M.B.**