*WINNER TAKE ALL?*

# CENTOCOR AND XOMA SQUARE OFF

NEW YORK—They have been billed as breakthrough products: the first monoclonal antibodies against sepsis, a sometimes deadly condition that can defy even the most powerful antibiotics. The rivalry between Centocor's (Malvern, PA) Centoxin and Xoma's (Berkeley, CA) E5 has been no less dramatic, spilling out of the laboratory and clinic into the courthouse and securities-trading floor.

Even before the U.S. Food and Drug Administration (FDA, Bethesda, MD) advisory committee hearing last month, the theatrics were getting pretty messy. Both E5 and Centoxin are designed to counter the deadly endotoxins released by gram-negative bacteria early in the cascade of events known as septic shock, and those similarities have given rise to a nasty patent fight. Information revealed in court this summer spurred trading in both stocks, with Xoma falling and Centocor rising in anticipation of the FDA hearing.

Wall Street reacted virtually instantly to the FDA advisory committee's okay of Centoxin and no decision on E5, boosting Centocor's stock price $3 to $40.50 on volume of 7.5 million shares, while Xoma's stock fell $5 a share to $15.50 on trading of 6.7 million shares. The betting now is that Centoxin will reap all the advantages of being first to market.

But it may be too soon to interpret the hearing as an all-for-Centocor, nothing-for-Xoma outcome. FDA committee members voiced misgivings about Centoxin that echo some of those expressed by doctors in the field, and Centocor has yet to win final approval for its product. The committee, meanwhile, proclaimed no clear obstacle to approving E5: the official version, at least, is that more time was needed to review Xoma's data.

Regardless of approval outcome, the makers of anti-endotoxin monoclonals can expect even fiercer competition ahead. The up and coming contenders: anti-TNF and anti-IL-1 products that promise effectiveness against a much broader range of infections.

**—Mimi Bluestone**

# DO PATENT TRIALS HURT MORE THAN HELP?

NEW YORK—Even before the FDA advisory committee meeting, arguments in the Xoma v. Centocor patent trial had soured some financial analysts on both companies. A gag order has prevented either side from discussing with outsiders Xoma's charge that Centocor's Centoxin infringes its E5 patent. But transcripts from the trial, under way since July in San Francisco, gave an unusually intimate glimpse of the companies' clinical data and communications with FDA well in advance of their appearances before the agency.

In court, each side saw its clinical statistics picked over with a fine-tooth comb. An attorney for Centocor reportedly accused Xoma President Patrick Scannon of having to "dredge through your data" to find some efficacy for E5, while a statistician hired as an expert witness for Xoma poked similar holes in the statistical significance of Centocor's data. Most analysts, however, drew the conclusion that Xoma's was the weaker data, since in its second Phase-III trial, a decline in morbidity failed to translate into a decline in mortality.

The crux of the matter, however, is Xoma's charge that Centoxin, a human/mouse antibody, binds to the same purified lipopolysaccharide as E5, a mouse antibody, competitively inhibiting E5 from so binding, as measured in enzyme immunoassay or other competitive-inhibition assay.

Despite all the numbers raked over in court, the jury may have to decide the case on the merits of whose assay looks more kosher. Centocor maintains that assays performed on its behalf show a lack of competitive inhibition, implying that its monoclonal binds to a different epitope and therefore does not infringe Xoma's E5 patent.

But biotech analyst David Stone of Cowen & Co. (Boston, MA) thinks that's hardly damning evidence. "Having the infringer say, I can't reproduce the experiment that I'm accused of infringing.' That's not convincing," Stone argues.

The trial probably will not rest until sometime in October, says a court official, but few observers think a jury verdict on such an esoteric matter will stand. Still, a jury decision favoring Xoma could enable the company to win an injunction that would upset Centocor's hopes of reaching the market immediately upon receiving FDA approval, Stone suggests.

Ultimately, Stuart Weisbrod, a biotech analyst at Merrill Lynch (New York), thinks the courts will grant Xoma a patent that covers just its mouse antibody, rather than all anti-endotoxin monoclonals. He cites the patent dispute between Amgen (Thousand Oaks, CA) and Genetics Institute (Cambridge, MA), in which the court narrowed Amgen's claim—that its patent covered erythropoietin (EPO) and EPO-like molecules—to cover only the company's EPO molecule. "That's a pretty strong precedent," Weisbrod says.

Whatever the verdict, the message for the industry should be to stay out of court where internal documents are bound to be exposed, argues biotech analyst Teena Lerner of Shearson Lehman Brothers (New York).

Lerner's misgivings about both products stem not only from the patent trial, but from clinicians' attitudes toward the drugs. For one thing, on July 23 the *New England Journal of Medicine* published eight letters questioning a February 14 report on clinical trials of Centoxin.

The letters show dissatisfaction with the Centoxin study—and the product—on several fronts. Clinicians are disappointed that the drug helps only patients whose sepsis or bacteremia is due to gram-negative bacteria, not other microorganisms, and aids only some of those patients.

One letter pointed to an "imbalance" among the placebo group, which was older and had a higher organ-failure rate than the Centoxin group. In fact, several doctors voiced concern that FDA might approve such an expensive drug without stronger proof of effectiveness or mechanism of action.

Of course, the drug's anticipated high cost is music to Wall Street's ears. In northern Europe, where Centoxin is already on sale, it goes for $3,500 per treatment. And Centocor, anticipating approval of the drug, says it expects to reach profitabilty sometime in 1992.

**—M.B.**